VOLUME 45 NUMBER 4, PART II APRIL, 1958

AMERICAN JOURNAL
OF
OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

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To Honor

SIR STEWART DUKE-ELDER

on the occasion of his

Sixtieth Birthday

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For a complete table of contents see pages 1 and 2

Subscription price in United States twelve dollars yearly. In Canada and foreign countries fourteen dollars. Published monthly by the Ophthalmic Publishing Company. Subscription and Advertising Office: 664 North Michigan Avenue, Chicago 11, Illinois. Entered as second class matter at the post office at Menasha, Wisconsic. Printed in U.S.A.

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CONTENTS

Sir Stewart Duke-Elder

STEWART DUKE-ELDER

> The true genius is a mind of large general powers, accidentally determined to some particular direction.
>
> Samuel Johnson,
> *Lives of the Poets* (Cowley) 1778.

This number of THE JOURNAL is a most special one, prepared with loving care and dedicated to Sir Stewart Duke-Elder on the occasion of his 60th birthday. It carries with it all good wishes, the admiration and deep affection from his many American friends, some of them contributors to this *Festschrift*. It is but a small measure of our love and gratitude to one who has done so much for ophthalmology, for medicine, and for his colleagues throughout the world. We pray that he will be spared to us many years, and continue to wax from strength to strength, for his strength is ours.

Duke-Elder was born in Dundee, on the Firth of Tay, Scotland, on April 22, 1898, the second of three boys. His father was a minister in the Free Church of Scotland. During Stewart's early school days, they lived at Kirkton of Tealing, a small village about five miles north of Dundee. We have a charming imaginary glimpse of him driving with his two brothers in a pony trap the five miles to school, very early in the morning, over rough roads, through the beautiful Scottish country side. His school was called Morgan's Academy. Here he was always at the head of his class, excelling in his studies to such a degree that he was awarded a handful of gold medals, the size of our silver dollars, so many in fact that, when stacked one on top of another, they look like a handsome stake in a poker game. Since then, and throughout his life, he has continued to collect medals for his many outstanding contributions, excellence, and brilliance of intellect.

His parents were good people of sterling character and strong faith and sternly upright as befits Godfearing. A Scotch Presbyterian Sabbath early in this century must have been a heavy burden for a boy of spirit, weighed down with the esoteric problems of prohibitions, predestination, sin, and free will. The thunderous frown of the ghost of John Knox was just above the benevolent eye of God and Big Brother was everywhere. But a good Fairy left over from the Renaissance undoubtedly leaned over Stewart's cradle and endowed him with its spirit, most fortunately for us.

Ten miles southeast of Dundee is St. Andrews. A prewar Baedeker has this to say about it:

> St. Andrews, a royal burgh of 8260 inhab., once the ecclesiastical metropolis of Scotland, is a picturesque and fashionable watering-place, freely exposed to the bracing breezes of the North Sea. It is, however, most famous as the Mecca of golfers, with its chief meetings in May and October. The Royal and Ancient Club, founded in 1754, is the governing power in the game. There are four courses; Old and New, Eden, and Jubilee. (Incidentally, the green's fees of Old are the most expensive, 2/6 before the war.) The university, founded in 1411 by Bishop Henry Wardlaw, consists of the colleges of St. Salvator (1450), St. Leonard (1512), and St. Mary (theological, 1537), the first two of which were formed in 1747 into the United College. The students (c. 600 in number) wear red gowns.

Graduating from Morgan's Academy with highest honors, Stewart went to the United College at St. Andrews to study medicine. There were only five choices of a career open for a lad from a financially pinched professional family. These were law, theology, engineering, armed services, and medicine. I do not know what influences were at work to have him choose medicine, no doubt the good Renaissance fairy played a part; but I do know that with his native intellect, alert mentality, and genius he would have made a successful career of any of these (except perhaps theology).

At St. Andrews he continued his brilliant promise. He was first Foundation Scholar in 1915; the British Association Medallist in 1915; Demonstrator of Physiology in 1918; University Scholar, 1919; Demonstrator of Anatomy, 1920; and President of the Student's Union and Representative Council,

Interallied conference, September, 1943.

1921. There are extant, stories of very funny college pranks that could be told here but only to show that at no time, then or now, was there anything dour or lugubrious about Stewart.

He was graduated M.A., with First-Class Honors, B.Sc., with Special Distinction, M.B., and Ch.B. in 1922; later the M.D. (Gold Medal) and the D.Sc. from St. Andrews, and the Ph.D. from the University of London in 1925. (All earned degrees.) In 1922 he went to the Royal Infirmary in Edinburgh as a House Officer.

In 1923 he set out for London with a pocket full of medals and diplomas and nothing else. To pay his way, he stopped off at Wellingborough, a town northeast of Northampton and about 70 miles from London. He served as locum tenans to a Dr. Arthur for a few months in order to earn a few guineas and then went on to St. George's Hospital, London, where he held positions as casualty officer, later house physician to Dr. Collier, house surgeon to Sir Crisp English, and resident anesthetist. Following this he was appointed to the staff of St. George's as junior ophthalmic surgeon and took his F.R.C.S. in 1924.

He soon came under the influence of Sir John Parsons. Stewart says, most movingly, in his obituary of Sir John (Brit. J. Ophth., 41:708, 1957):

> To him I owe everything; he taught me ophthalmology and made possible anything I may have done professionally. He was indeed a great man, massive in physique and mind, inexhaustible in his capacity for work, and rock-like in his intellectual honesty.

I know that Sir John loved Stewart as his favorite pupil and friend, and we can say that as the twig is bent so is the tree.

While in the "house" at St. George's, Stewart did clinical research on diabetes under a grant from the Medical Research Council at University College (London) and began his investigations on intraocular fluids, for which he received the 1926-1927 Sir Francis Laking Prize from the Biochemical Department, St. George's Hospital. He chose as the motto for his monograph, "The nature of the intraocular fluids," published under the auspices of the *British Journal of Ophthalmology*, a quotation from Horace:

> Nullius addictus jurare in verba magistri.

And a quotation from Sir John Parsons

Interallied informality, April, 1944. Duke-Elder and Derrick Vail.

that has stayed with Stewart all these years:

> Progress in Ophthalmology must depend upon the application of new discoveries in chemistry and physics.

In this year (1927) there also appeared the first edition of his book, *Recent Advances in Ophthalmology*, published by J. & A. Churchill, London, in which he gives us a preview of his great genius and ability in collecting, collating, weeding out, and most lucidly rewriting with acute discrimination, the important and essential advances of our science as reported in the literature to that time.

In 1928 he fortunately married Phyllis Mary Edgar of London and, in their haste to get away from it all, the young couple departed for their honeymoon without their luggage.

Lady Duke-Elder is a person of great distinction in her own right. She was graduated M.B., B.S., from the University of London in 1926 and became M.R.C.S. (Eng.) and L.R.C.P., London, in 1926. She is on the Staff, as an ophthalmologist, of the University College Hospital, London. Her other positions and appointments include research, Medical Research Council, Department of Physiology, University College; chief clinical assistant and medical officer, Royal London Ophthalmic Hospital (Moorfields); and medical officer, British Red Cross Society Auxiliary Hospital at Baustead. She is a Dame in the Order of the Knights of St. John and an honorary member of the Association for Research in Ophthalmology. She has sublimated the demands of her professional career to stand at the side of her husband and to assist him in every way. They make a perfect team, a harmonious and devoted couple, whose peaceful, happy, and hospitable home life, so essential for great accomplishment, is an inspiration to those privileged to share in it. Stewart would be the first to admit that much of the credit for the growth of his genius goes to her. We who know salute and love her and cherish her fortitude and cheerful courage in the face of the serious illness that has been a thorn and a handicap for so many years.

Brigadier to the Front, October, 1944.

On their return from their wedding trip, the Duke-Elders first settled at 59 Harley Street, a few doors south of their present abode. In 1933, they moved to 63 Harley Street, the most famous address in ophthalmology and a Mecca for all ophthalmologists and even their wives, sons, and daughters. In this world famous medical street, the Duke-Elders worked and practiced and collaborated in research and joint contributions to our literature and Stewart prepared his *Textbook*. As side lines, he brought out his *Recent Advances*, collaborated with Sir John Parsons in the latter's well-known *Diseases of the Eye*, and wrote the delightful and surprising *Practice of Refraction* which has gone into six editions, as well as continuing his sound researches in ocular physiology, especially the intraocular fluids, and publishing in a steady stream his results that have had great influence. His enormous knowledge, energy, alert mind, and skill of expression drove him on and on. And it was not unusual for him to write steadily through the night, then begin an arduous day with-

On the way to the Front, October, 1944. Duke-Elder with United States G.I. driver.

out sleep. Time-wasting hobbies, such as cards, tennis, or golf, did not interest him. He took pleasure in the company of dear friends and an occasional convivial dinner party or the theater. No spare moment was wasted, however, and his quick mind was seldom away from his work. Yet, during this time he collected and enjoys his beautiful paintings, works of art, and first editions, so that his home now is truly a treasure house, fortunately spared in the bombings of World War II.

His creative work was seriously interrupted by World War II. He was appointed first a colonel in the R.A.M.C., and later a brigadier, serving from 1940-1946 as Chief Consultant in Ophthalmology in the War Office. His time was occupied with matters of ophthalmic supply, personnel, circular orders, directives, various military boards and committees, military travel, consultations, and so forth. His services were of immeasurable help to the Medical Department, U. S. Army, and his cordial friendships with the United States ophthalmic medical officers stationed in England will never be forgotten by them. He was a boon companion and a most cheerful friend. His puckish humor is a joy to experience, and I recall with enormous satisfaction, many an extracurricular "calliathump" that we enjoyed together in those otherwise trying days of frustration and red tape. His glee at the destruction of most of the official Army records in the War Office by a German bomb is a cherished memory.

Although his war efforts consisted of outstanding contributions to the success of the work of the R.A.M.C. in all theaters of action, his achievements and those of his medical colleagues were not, most regrettably, recognized nor rewarded by the higher brass in the Regular Army, bad cess to them. It is therefore with considerable pleasure to record that our Government awarded him the Bronze Star for his great help to us prior to D-day.

Since the war he has completed the seven volumes of his chef d'oeuvre and has started on the second editions of them. Besides this, he continues his other studies, particularly directing the research of the Institute of Ophthalmology of London, a cherished dream of his that has come true, and which under his direction has developed world-wide influence and prestige. He has traveled throughout the world, lecturing and teaching ophthalmology, at least four or five times to this country. Wherever he has gone he has made innumerable friends for life and has brought the inspiration of his great mind and genius personally to most all of us everywhere. He planned and developed a new eye hospital for clinical care and research in Jordan for which he received the highest decoration from that country's sovereign. Unfortunately, the recent serious troubles in the Middle East have prevented the fruits of this work from developing as they should, and this is a source of keen disappointment to him.

If you will look at Duke-Elder's list of published contributions, you will readily see how much he has done for us and for our patients. There is scarcely a part of our science to which he has not made an original

Above: Ascot Gold Cup Races, 1957.

Below: Proper auto license for an ophthalmologist.

and noteworthy contribution. His experimental researches excel, if possible, his clinical acumen, contributions, and surgical skill. He is truly a universal ophthalmologist. His most important gift to us is his seven-volume *Textbook of Ophthalmology* that is our Bible and inspiration. This monumental and extraordinary work is essentially his own, for little or no outside help was received in its preparation. It was written entirely in longhand and required an overwhelming scope of knowledge of every phase of ophthalmology and general medicine, but particularly an astounding ability to pick out, assemble, and judge the proven facts and theories of our great specialty, and express them in most lucid and flowing prose that is a joy to read and study, and easy to fix in our minds. Happy and fortunate, indeed, are the beginners in ophthalmology who now have access to this fabulous storehouse and treasure of this Aladdin of ophthalmology.

It is a pleasure to note the many honors and awards that have come to this man, given by a grateful scientific world for his gifts. Here are some of them, copied for the most part from *Who's Who of Great Britain*. The list is not complete, nor will it be until his end; for in spite of his recent desire to relax and devote his time to the cultivating and enjoyment of nonophthalmologic things, such as general literature, the arts, the theater, and, above all, dear friends, his demon will not permit him this leisure I am sure, so we look forward to more expression of his ophthalmic genius as time unfolds.

Peace-time International Glaucoma Conference, Montreal, September, 1954. Malbran, Duke-Elder, Scheie, Kinsey.

DUKE-ELDER, Sir Stewart, G.C.V.O. cr. 1958, K.C.V.O., cr. 1946; Kt., cr. 1933; Hon. F.R.C.S. Edin. 1950; Hon. D.Sc. (Northwestern, McGill), Hon. M.D. (Dublin), D.M. (Utrecht, Strasbourg, Ghent), LL.D. (St. And.); Hon. F.A.C.S.; Hon. Colonel R.A.M.C.: Bronze Star Medal (U.S.A.); Surgeon-Oculist to the Queen since 1952 (formerly to King George VI); Hon. Cons. Ophthalmic Surgeon to the Army; Civilian Ophthalmic Consultant to the R.A.F.; Adviser in Ophthalmology, Ministry of Health; Director of Research, Institute of Ophthalmology, University of London; Ophthalmic Surgeon, St. George's Hospital, London; Consulting Ophthalmic Surgeon, Moorfields Eye Hospital; Hon. Ophthalmic Surgeon, Alexandra Orphanage; Fellow University College, London; President International Council of Ophthalmology; Past Pres. Faculty of Ophthalmologists; lately Vice-Pres. Ophthalmological Society United Kingdom; Hon. Member: American, Australian, Canadian, French, Belgian, Danish, Swedish, Dutch, Greek, Pan-American, Mexican, and New Zealand Oph. Societies; Association for Research in Ophthalmology (U.S.A.); Roy. Soc. Sciences, Upsala; Consultant Nat. Soc. Prevention of Blindness, U.S.A.; Hon. Fellow American Medical Association; Hon. Fellow American Academy of Ophthalmology and Otolaryngology; Hon. member Pan-American Medical Soc.; Hon. member Alpha Omega Alpha (U.S.A.); Pres. Council International Federation Ophth.; Pres. XVI Internat. Cong. Ophth. London, 1950; Henry George Plimmer Research Fellow, 1925; Sir Francis Laking Research Scholar, 1926-29; Paul Philip Reitlinger Prizeman, 1926; B.M.A. Scholar, 1927; B.M.A. Middlemore Prizeman, 1928; William Mackenzie Memorial Medallist (Glasgow), 1929; Research Associate, U.C., London, 1930; Howe Lecturer in Ophthalmology, Harvard Univ., U.S.A., 1930; Nettleship Medal for Research in Ophthalmology, 1933; Howe Medallist, Amer. Ophth. Soc. (U.S.A.), 1946; Research Medallist, Sect. on Ophth., Amer. Med. Asso., 1946; Donders Medallist (Holland), 1947; Doyne Medallist, Oxford, 1948; Proctor Lecture, U.S.A., 1951; Gullstrand Medallist (Sweden), 1952; Craig Prizeman (Belfast), 1952; Medallist, Strasbourg Univ., 1952, Ghent Univ., 1953; Gonin Medallist (International), 1954; Bowman Medallist (Ophth. Soc. U. Kingdom), 1956; Lister

Medallist (R.C.S.), 1958. Examiner in ophthalmology, Royal College of Surgeons, 1947-51; Editor, *Ophthalmic Literature;* Chairman Editorial Board, *British Journal of Ophthalmology.* Hospitaller, Order of St. John; K.G.St.J.

I have tried to give here some idea of the two Stewart Duke-Elders, the scientist and the man, both of them modest and straightforward, but surprisingly different, for the one, judged from his writings, gives the impression of being very old, articulate, lucid, infinitely wise and learned; the other is youthful, exuberant, a delightful companion, far from austere; hospitable, generous, cosmopolitan, democratic, friendly, intellectual, earthy; a person with whom you get on a first-name basis, no matter what language you speak, straight away. We love both of him.

Samuel Johnson, in speaking of his *Dictionary* (Boswell's Life, Oct. 10, 1779) said:

> I knew very well what I was undertaking, and very well how to do it, and have done it very well.

The same can be said of Stewart and his life's work.

Happy Birthday, Stewart, and God Bless you.

Derrick Vail.

FOOTNOTE: Most of the facts as outlined here were obtained, sub rosa, from P. M. Duke-Elder, since this issue was planned to be a birthday surprise. She wrote: "Incidentally, I have been semi-open to S. about this, to get the dates, telling him it's a pre-obituary—his reply being—'He's (D.V.) just one of those——Editors.' . . . It's O.K. and he hasn't a clue." (D.V.)

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THE USE OF TENON'S CAPSULE IN STRABISMUS SURGERY

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On several occasions I have used strips of Tenon's capsule to align the eyes when one of the ocular muscles could not be found. The first time I did this was to correct a defect caused by my own carelessness in accidentally cutting an inferior rectus muscle in place of an inferior oblique. I have since used the same operation on two other patients to correct exotropia produced by other surgeons as a result of tenotomy of the medial rectus muscles in children with esotropia. In the belief that others will sometimes find themselves in similar embarrassing positions I am reporting this operation as it was done on these three patients.

CASE REPORTS

CASE 1

S. M., a girl, aged six years, was first seen in December, 1945, with a history of either eye turning in since the age of three years. The right fissure was slightly narrower than the left, with a slight ptosis. There was an incomitant esotropia. Fixation was generally carried out with the left eye. When fixating with the left eye there was an esotropia of 20 prism diopters with a left hypertropia of 10 prism diopters. When fixating with the right eye there was an esotropia of 20 prism diopters with a left hypertropia of 30 prism diopters. In addition, there was marked overaction of the left inferior oblique muscle in gaze up and to the right, but no similar overaction of the right inferior oblique on gaze up and to the left. There was no head tilt and no Helmholtz-Bielschowsky sign on tilting the head to either shoulder. The refraction under atropine was:

R.E., +0.75D. sph. $\bigcirc$ +0.5D. cyl. ax. 45° = 6/10; L.E., +0.75D. sph. $\bigcirc$ +0.5D. cyl. ax. 135° = 6/10. There was no family history of strabismus, and birth was normal. On the basis of these findings a diagnosis was made of congenital paralysis of the right superior rectus muscle with esotropia on the basis of sensory dissociation.

As a primary procedure it was planned to do a bilateral retroplacement of the medial recti and a myectomy of the left inferior oblique. This was done on June 5, 1946, under general anesthesia. The operative notes, exactly as they were recorded by the senior resident, follow:

"The internal rectus on the right side was isolated and recessed in the usual manner three mm. The left internal rectus was exposed and cut from its attachment. A muscle hook was then passed down through the same incision that the internal rectus was isolated in an attempt to get the inferior oblique on this side. The inferior oblique was raised inclosed in its sheath, and this was opened in an attempt to free it from the internal rectus. This was thought possible, and a section of the muscle was cut out. The internal rectus was then sutured to its new position three mm. back of the original insertion. At this time it was evident that the left eye was deviated upward from 15 to 20 degrees. There had been some bleeding in cutting the inferior oblique, and it was a question whether the hematoma thus produced had caused the upward tilt. However, it was felt advisable to explore the inferior rectus, thinking that this might have been cut accidentally. An incision was made through the conjunctiva over the insertion of the inferior rectus and a hook was passed down in an attempt to pick up the inferior rectus. It was now seen that this had been accidentally cut. The insertion was grasped and the muscle was picked up below and brought up and sutured to the insertion. There had been so much bleeding in the tissues that identification of the actual muscle was not possible.

"At the end of the operation the eyes were divergent some 15 degrees and the left was up some 10 to 15 degrees. Both eyes were closed after a general prayer had been offered by everyone present."

On June 21, 1946, the record states that the lateral deviation was corrected, but a definite left hypertropia was still present. On October 5, 1946, the left hypertropia measured 25 prism diopters and the left eye looked proptosed. Exophthalmometer measurements showed that this was only apparent, however, as each eye measured 16 mm. with a baseline of 88 mm. The conjunctiva over the site of the inferior rectus had now become considerably hypertrophied and bulged forward, so that it was constantly exposed, even when the lids were closed. As a result of this it had become dried and keratinized.

On October 7, 1946, the inferior rectus site was again explored under general anesthesia. Considerable scar tissue was removed, but the inferior rectus could not be positively identified. The inferior oblique, however, was identified and cut. A band of Tenon's capsule having the direction like that of the inferior rectus muscle was fashioned into a tongue and brought forward as far as possible. While it was under tension a double-armed suture was placed through the original insertion of the inferior rectus and brought through the tongue of fascia in such a position that when this suture was tied the globe was brought down into vertical alignment with the right eye or slightly below this. The excess of Tenon's capsule was then excised and the conjunctiva closed. This re-

Fig. 1 (Adler). *Case 1, S. M.* Postoperative. (a) Looking up. (b) Dextroversion. (c) Primary position. (d) Levoversion. (e) Looking down. There is good alignment in all positions of gaze except in (a) where movement of the left eye is restricted.

sulted in an immediate correction of the vertical deviation, and the eyes have remained in good alignment since then.

By 1949, at the age of nine years, she had binocular single vision with stereopsis and good bar reading. She had four prism diopters of esophoria and four prism diopters of left hyperphoria for distance, and the correction for the hyperphoria was ordered for her with prisms in her glasses. There were seven prism diopters of esophoria and three of left hyperphoria for near. On October 11, 1954, she had one prism diopter of left hyperphoria and was entirely comfortable with the following correction:

R.E., −0.50D. cyl. ax 45° combined with 0.5 prism diopter base-up; L.E., +0.50D. sph. ⊃ 1.25D. cyl. ax. 75° combined with 0.5 prism diopter base-down. Vision 6/6 in each eye with correction.

On November 27, 1957, her vision was normal in each eye with the following correction: R.E., +0.25D. sph. ⊃ −0.75D. cyl. ax. 120° combined with 1.0 prism diopter base-up; L.E., +0.5D. sph. ⊃ −1.5D. cyl. ax 75° combined with 1.0 prism diopter base-down.

The right fissure was slightly narrower than the left. The eyes were in good alignment in the primary position both horizontally and vertically (fig. 1). There was good alignment in versions in the down positions. There was marked restriction of movement of the left eye up and to the right or left due to a combination of the myectomy of the left inferior oblique and restrictive force of the tongue of capsule which was anchored to the globe (fig. 2). The inferior rectus muscle must have been contained in this tongue of fascia; otherwise we cannot account for the good motility of the left eye down and left.

Case 2

Mr. R. W., aged 32 years, was first seen April 7, 1955, with a marked divergent strabismus, requesting cosmetic surgery to straighten his eyes. These had been divergent since an operation performed to correct a convergent squint by another surgeon at the age of six. Visual acuity: R.E. = 6/6; L.E. = counting fingers at 1.0 m. without glasses. His refraction was a low hyperopic astigmatism. Fundi were normal. In addition to the divergent strabismus of approximately 60 prism diopters in the primary position of gaze there was a complete paralysis of the left medial rectus muscle (fig. 3). Ductions of the right eye were normal, but the left eye could not be moved to the right beyond the midline. Ductions in other directions were normal. There was no vertical element present in the strabismus.

It was evident that the left medial rectus had either been completely tenotomized or had slipped

Fig. 2 (Adler). *Case 1, S. M.* Postoperative. Same case as in Figure 1. (a) Looking up and right. (b) Looking up and left. (c) Looking down and right. (d) Looking down and left. There is good alignment in downward gaze but in looking up and to the right and to the left there is marked restriction of movement of the left eye.

from its attachment after being retroplaced. I told the patient that by means of surgery I could bring his eyes into parallelism in the primary position by utilizing a strip of fascia if I failed to find the cut medial rectus muscle, but that if I did so he would have a convergent squint when he looked to the left, and when he looked to the right the left eye would not move beyond the midline any more than it did now. I made sure that he understood the only cosmetic improvement would be that his eyes would be straight, or nearly so, in the primary position of gaze. He understood the situation, and accordingly on April 13, 1955, I explored the left medial rectus under pentothal anesthesia. The muscle could not be found. Accordingly, a strip of Tenon's fascia over the site of the medial rectus muscle was pulled forward and fashioned into a tongue and fastened to the globe approximately at the normal insertion of the medial rectus muscle with a whip suture 4-0 chromic gut (fig. 4). At the conclusion of this procedure the eyes were straight under the anesthetic. Both eyes were bandaged with antibiotics. At the first dressing done on the second postoperative day there was very little reaction, and the eyes were found to be entirely straight, not only in the primary position of gaze, but also in both levo- and dextroversion, which were well carried out. This result was more astounding to me than to the patient. Apparently by luck, the medial rectus muscle, or what remained of it, was included in the tongue of fascia which I had utilized, and when this was attached to the globe the function of the muscle was restored, as shown in the photographs (fig. 5).

The patient was last seen on September 7, 1956. His eyes have remained straight, and he has excellent dextro- and levoversion.

CASE 3

Mr. S. C., aged 53 years, was first seen September 13, 1955, giving a similar history to the last patient. As a child he had a convergent strabismus, was operated on twice when he was approximately five years of age, and the final result was a very disfiguring divergent strabismus which he was anxious to have cosmetically corrected. I told him of the first patient, but assured him that it was just luck that this patient got movement of his eyes in addition to their being straight in the primary position, and that all he could hope for was a good cosmetic result in the primary position of gaze.

Examination showed a divergent strabismus of approximately 60 prism diopters in the primary position of gaze. Fixation was maintained with

Fig. 3 (Adler). *Case 2, R. W.* Preoperative, April 11, 1955. (a) Dextroversion: left eye cannot move even to the midline. (b) Primary position, showing marked exotropia. (c) Levoversion: fair alignment.

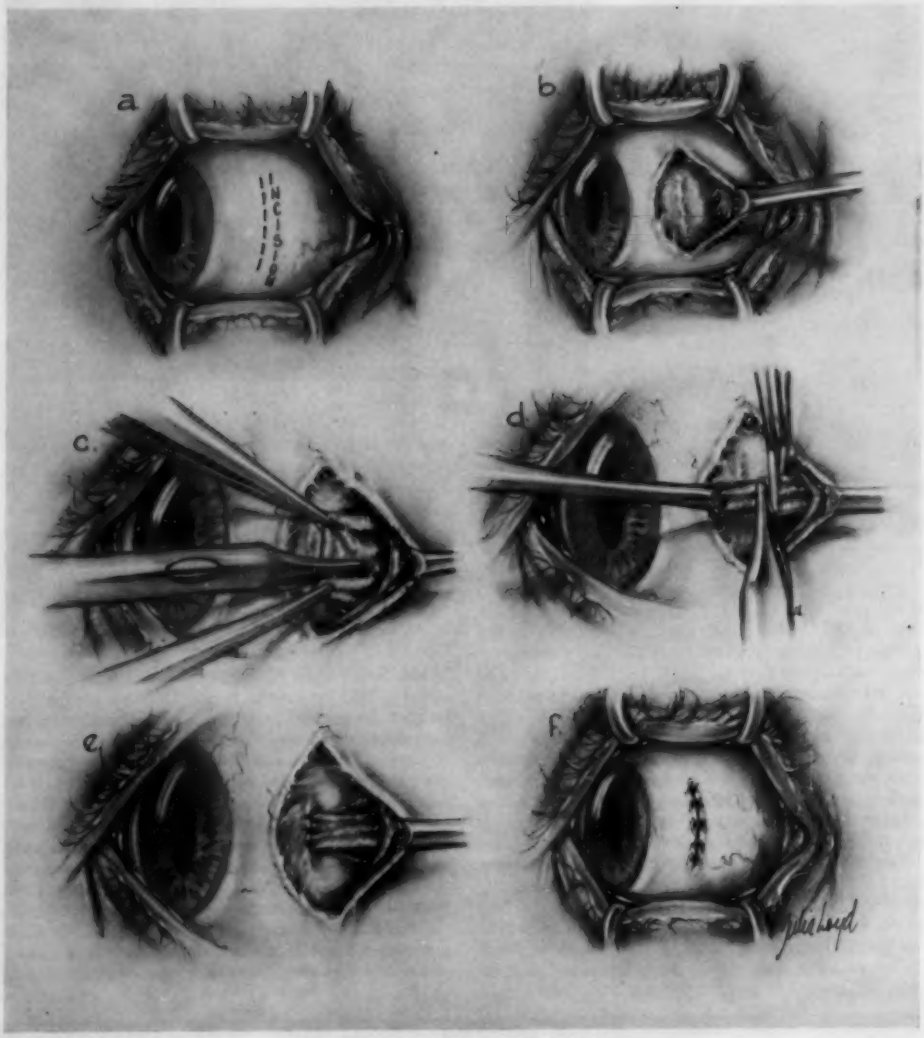

Fig. 4 (Adler). *Steps in the operation.*

a. Conjunctival incision over insertion of medial rectus.
b. Exposure of the insertion and scar tissue but no muscle.
c. Double layer of Tenon's capsule brought forward and cut with scissors along two parallel lines forming a tongue.
d. Extension of this tongue deep in the orbit, brought forward and put on tension. Excess of anterior end cut off.
e. Suture of tongue to original insertion of muscle.
f. Closure of conjunctiva.

Fig. 5 (Adler). *Case 2, R. W.* Postoperative. Same patient as in Figure 3. (a) Dextroversion. (b) Primary position. (c) Levoversion. Good alignment and motility in all positions.

the left eye, but when the left eye was covered the right could fixate. There was a complete paralysis of the right medial rectus muscle, and the right eye could not be moved beyond the midline in levoversion. No other muscles were involved. The visual acuity with best correction was: R.E. = 6/100; L.E. = 6/6.

On September 21, 1955, under general anesthesia the right eye was prepared and draped in the usual manner. A muscle hook was inserted in the medial canthus and the globe was drawn medially, and it was noted that there did not appear to be any fibrosis of the lateral rectus muscle by this forced duction test. The conjunctiva overlying the medial rectus muscle was then incised, a muscle hook inserted, and a small atrophic medial rectus muscle isolated. The relatively few fibers were freed from their insertion on the globe, and held, together with the surrounding fascia, in a Prince clamp. A tongue of Tenon's capsule was then fashioned, including the muscle fibers, and this was anchored on the globe at the normal insertion after the globe had been rotated nasally so that its visual line was slightly convergent to that of the fellow eye. The tongue of fascia was freed from the check ligament before it was pulled forward to be attached to the globe.

At the first postoperative dressing two days later the eyes were much straighter than they were before operation, but they were not in exact alignment, and while the right eye could move slightly beyond the midline in levoversion, the excursion was limited. Five days later the result was the same, but during the next two months the divergence of the eyes in the primary position increased. By November 28, 1955, I advised reoperation.

On November 30, 1955, under intravenous pentothal the right lateral rectus muscle was recessed four mm., and the medial rectus and tongue of Tenon's fascia explored. This was dissected free from its attachment to the globe, drawn further forward, and anchored at the insertion further back, about five mm. from the original location of the suture. This produced good alignment and excellent motility in all directions. Following the operation the patient complained of some diplopia, but this gradually disappeared. He was last seen on March 6, 1957. The eyes were in good alignment and versions were well carried out (fig. 6). He has no diplopia.

Comment

In these three cases the use of a strip of Tenon's fascia corrected disfiguring surgical

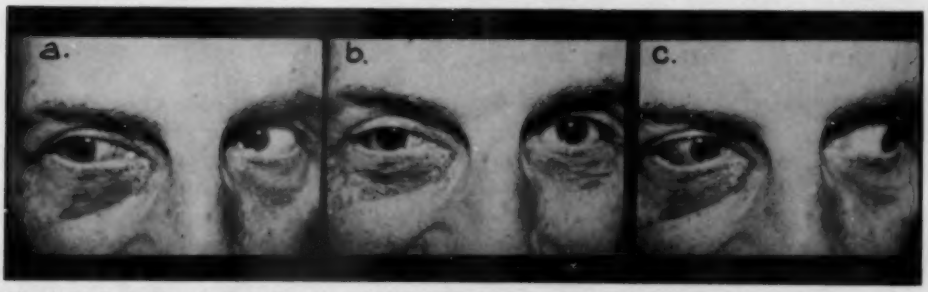

Fig. 6 (Adler). *Case 3, S. C.* Postoperative. (a) Dextroversion. (b) Primary position. (c) Levoversion. Good alignment and good motility.

mistakes as a result of which the function of a muscle had been previously destroyed. There are other conditions in which this procedure might be indicated, although I have had no personal experience with them. Although rare, cases of congenitally absent muscles have been reported. Absence of the inferior rectus muscle has been found by a number of authors. Casten (Casten, V.: Isolated congenital absence of the inferior rectus muscle. Arch. Ophth., **24**:55, 1940) has reported two such cases, and cites the literature up to that time. In both of his cases he reported good results with a modified Hummelscheim operation; in the first utilizing half of the lateral rectus muscle transplanted to the site of the insertion of the inferior rectus. In the second case, transplantation of half of the medial and half of the lateral rectus muscles was done, each muscle being operated on at a separate occasion. This procedure seems much more complicated than that which I have used, and it seems to me that the simpler procedure should be tried first.

Hill (Hill, H.: Absence of the medial rectus and its successful treatment by vertical tendon transplants. Tr. Am. Ophth. Soc., **53**:115, 1955) reports the absence of a medial rectus muscle and its successful treatment by employing transplantation of half of the superior and half of the inferior rectus muscles to the site of the medial rectus. The medial rectus in this case had been destroyed by previous surgery for a tumor in this situation. The Hummelscheim technique has been used extensively for sixth nerve paralysis, but Hill's case was the first in which this procedure has been reported in patients with paralysis or absence of the medial rectus muscle.

SUMMARY

In three cases of strabismus where muscles had been accidentally destroyed surgically, repair of the damage was successfully effected by the use of a tongue of Tenon's fascia brought forward at the site of the destroyed muscle. In all three cases excellent cosmetic results were achieved, not only in bringing the eyes into alignment in the primary position of gaze, but in enabling the eye to carry out versions in the direction of action of the severed muscle. Evidently the muscle tissue had not been destroyed, and was included in the tongue of Tenon's capsule, which was attached to the globe. This procedure should be tried in all cases of defective motility either due to previous surgical destruction of a muscle or where the muscle is congenitally absent.

313 South 17th Street (3).

THE ETIOLOGIC DIAGNOSIS OF UVEITIS

ACCORDING TO CLINICAL FINDINGS OVER A 10-YEAR PERIOD

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The purpose of this paper is to show the results of my efforts in establishing the etiologic diagnosis of uveitis in different series of patients in which I endeavored to establish this diagnosis by making thorough investigations according to the means at my disposal at different times during the last 10 years.

The establishment of the etiologic diagnosis in cases of uveitis is obviously of paramount importance. The great discrepancies which can be found by reading the world literature make the publication of papers dealing with larger series of cases important. Usually in such papers the utmost efforts are made to find out which of several etiologic factors were present. It is only through such publications that the facts will come to

light and the general consensus will gradually be changed.

It is a known fact that there are "schools" of thought regarding the etiology of uveitis. In Europe tuberculosis is still considered to be the main cause. Focal infections which cause the allergic nongranulomatous uveitis are in a way still a novelty and, only as late as 1956, four cases of uveitis caused by tonsil infection were presented at a highly regarded annual meeting of a national ophthalmologic society with the implication that this etiology was worthwhile reporting.

My first series comprises 175 patients with chronic endogenous uveitis. In that series of patients, examinations were made for the following etiologic factors: syphilis and tuberculosis. For syphilis diagnosis the patients were sent to a syphilologist who in turn ordered the laboratory tests he thought might be most useful in each case and then reported back to me. In regard to the search for tuberculosis, the patients were sent to a phthisiologist who ordered the tests he deemed necessary in each case and then reported to me.

Examinations for the detection of foci were done as follows: for the examination of tonsils and paranasal sinuses the patient was sent to an otorhinolaryngologist. For an examination of the teeth the patient was asked to have X-ray studies of all his teeth and then was sent to a dentist for further clinical examination and interpretation of the findings. The intestinal tract, comprising appendix, gall bladder, and so forth was examined by a specialist who asked for all the complementary examinations and reported back. The urogenital tract was likewise examined by a specialist in this field who asked for complementary examinations and then reported back.

As a result of these examinations the following percentages were found: syphilis 5.71 percent, tuberculosis 6.14 percent, lymphogranuloma venereum 0.57 percent, sine causa 19.37 percent. Regarding the foci, the findings were: infected teeth, 52.57 percent, infected tonsils 43.43 percent, infected

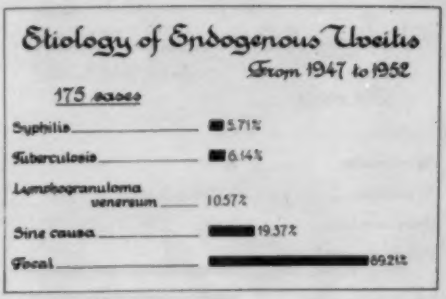

Fig. 1 (Alvaro). Findings in the first series of cases.

sinuses 16.57 percent, intestinal tract, including appendix and gall bladder, 17.71 percent, genitourinary tract 4.57 percent. In many cases there were several foci, consequently there is an overlapping of the percentages (fig. 1).

In a second series of 394 patients, the same procedures were followed in looking for the etiology. In addition skin sensitization and complement fixation tests were made for brucellosis and for toxoplasmosis. Feldman's technique of injecting emulsions of tissue and blood of the suspected patient into mice, intraspinally, intracerebrally, and intraperitoneally, was used. Intracutaneous sensitization tests were also made for streptococci which are pathogenetic for human beings.

In this series of 394 patients with uveitis the etiologies showed the following percentages: syphilis 1.0 percent, tuberculosis 5.1 percent, brucellosis 1.3 percent and toxoplasmosis 0.5 percent. Positive skin sensitization tests for streptococci pathogenetic to humans were found in 92.1 percent of cases (fig. 2).

Of the 363 patients in whom there were positive skin sensitization tests for streptococci pathologic to humans, 292, or 74.1 percent showed evidence of having actual foci which were detectable by the methods of examination already mentioned. In the 71 remaining cases, actual foci were not found but the positive skin test for streptococci showed evidence that the etiology was of a streptococcal nature.

In the last series all patients were tested

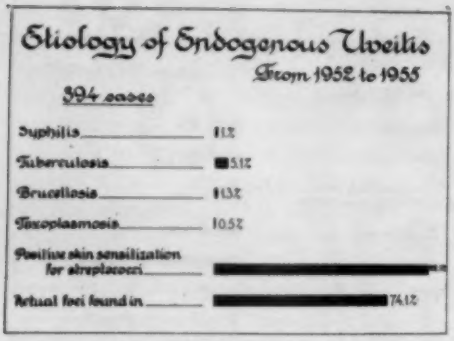

Fig. 2 (Alvaro). Findings in the second series of cases.

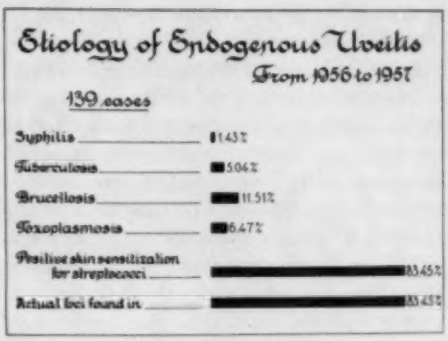

Fig. 3 (Alvaro). Findings in the third series of cases.

for syphilis, tuberculosis, brucellosis, toxoplasmosis, and skin sensitization for the streptococci which are pathogenetic to humans. In addition each patient was examined for foci in teeth, tonsils, intestinal tract, including appendix and gall bladder, genitourinary tract, and paranasal sinuses.

The chief difference between this series of 139 cases and the two previous series is that, for this group of patients, it was possible to have dye tests and complement fixation tests done at intervals of 30 days. The cases which were regarded as positive were only those in which the dye test was positive at first, at least at 1:68, while at the same time the complement fixation was negative, and 30 days later the titer of the dye test was higher and the complement fixation test became positive, a criterion advocated by Sabin.

The results were: syphilis 1.43 percent, tuberculosis 5.04 percent, brucellosis 11.51 percent, and toxoplasmosis 6.47 percent. In 116 cases there were positive results for skin sensitization tests for streptococci and actual foci were found in all these cases (fig. 3).

In 11 cases in which the etiology was definitely of the granulomatous type there were positive skin sensitization tests for streptococci; however, in all of these cases an actual focus was never found.

Using Sabin's criterion for establishing a positive toxoplasmosis diagnosis the percentage with toxoplasmosis as an etiology reached 6.47 percent of all cases in the series, the highest percentage found in any of the three series.

Analyzing these different series of cases two main facts stand out:

1. The possibility of establishing an etiologic diagnosis in the first series was limited by the facilities available at that time, consequently, this series is not comparable statistically.

2. There were variations in percentages of the different etiologies in the different series, although the same methods of examination were used in all; thus, there are definite discrepancies in the comparable statistics.

It is to be concluded, therefore, that in order to have a true picture of the etiology of uveitis, even considering its incidence in one single place, standardized methods of diagnosis are essential. It would seem desirable to standardize the methods for the etiologic diagnosis in uveitis and then seek the co-operation of different centers in which these methods would be applied for a period of years. This would provide comparable statistics and give more accurate information on the prevalent causes of uveitis.

Summary and Conclusions

For a period of over 10 years, in three series totalling 708 patients with chronic endogenous uveitis, different tests were made

to establish the etiology. These series are only partially comparable but the results show that efforts should be made to standardize the methods of diagnosis and have these methods applied in many clinics throughout the world, thus enabling world ophthalmology to have a true picture of the etiology of uveitis.

1151 Consolação.

OCULAR LESIONS RELATED TO DISTURBANCES IN FAT METABOLISM*

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In the protective environment of an antibiotic age, the lowering incidence of infectious diseases and the lengthening life span have unmasked and emphasized the importance of disorders of metabolism.

Ophthalmologists find increasing concern with this problem. Investigators in other fields of medicine, casting about for clues which may help in the understanding of the over-all picture of many of the so-called degenerative diseases so intimately associated with aberrations of fat metabolism, are learning that many ocular lesions, previously considered only in relation to ocular function, are frequently indicators of more serious and widespread disorder. Careful observation and proper interpretation of these signs may offer important contributions to the clarification of the disease process.

To maintain a place in the unfolding picture of metabolic disorders, the ophthalmologist must be competent in the recognition and classification of a given ocular lesion. More than this, any contribution to the understanding of the underlying primary disorder, of which this lesion may be only one of many manifestations, requires some familiarity with the basic biochemical processes involved.

A working knowledge of these processes is indeed mandatory for the development of a sphere of interest mutual to the pediatrician, internist, or neurologist. Studied with the combined resources of such a group the ocular lesion, which may have seemed so baffling and mysterious when viewed within the limited perspective of the speciality, becomes more interesting, informative, and rewarding to all concerned.

The clinical ophthalmologist, either because of inadequate training or because of a fundamental ingrown antipathy to the complexity of structural formulas and the technical jargon with which we have been confounded by our chemically minded colleagues, is many times poorly conditioned for such a co-operative effort.

It is hoped that this paper will be of particular interest to this group. Perhaps to them, as to the senior author of this paper, ocular lesions characterized by the presence of abnormal amounts of fat have been considered as a heterogeneous group, unorganized; except for the presence of fat as a common denominator, unrelated; and except for such connotation as might be derived from the name applied, poorly understood.

If so, we may at least anticipate a sympathetic understanding of our efforts here, with the aid of colleagues from the departments of pathology and medicine, to assimilate and bring some order into a confusing picture, to appraise our concepts of ocular diseases associated with aberrations in fat metabolism in the light of recent advances in the knowledge of this function, and, insofar as possible, to pin down this hazy, poorly defined, and unorganized information into an orderly arrangement, the hard core

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TABLE 1

LIPID CONSTITUENTS OF HUMAN PLASMA

Total lipid (all fat or fatlike substances)	570 mg./100 ml.
1. Neutral fat (fatty acids combined with glycerol)	90 mg./100 ml.
2. Phospholipids (fatty acids, phosphorus and a nitrogen containing substance). Important phospholipids are the (a) lecithins, (b) cephalins, (c) sphingomyelins	240 mg./100 ml.
3. Cholesterol esters (cholesterol combined with fatty acid)	140 mg./100 ml.
4. Total cholesterol (free cholesterol plus esterified cholesterol)	194 mg./100 ml.
5. Free fatty acids (bound to albumin) (after Peters and van Slyke)[1]	10 mg./100 ml.

of which, presented in elementary form, may be available and useful for ophthalmologists who may meet with similar problems.

An orderly assimilation and understanding of ocular lesions associated with derangements in fat metabolism, the so-called lipidoses, requires some familiarity with the practical aspects of lipid chemistry and physiology. While the exact combinations in which these lipids exist in the plasma is not definitely known they are generally separated as shown in Table 1.

Normally all the fat is bound to protein in the form of macromolecules called lipoproteins. Because of the technical ease with which it may be measured, cholesterol in the serum is the component most extensively studied. While the determination of the serum cholesterol alone cannot be considered adequate for investigative procedures such a determination does within limits indicate proportionate changes in the other lipids of the serum, since all fractions tend to vary simultaneously in the same direction.

As a general rule only lesions which occur bilaterally are associated with systemic disease. The monocular accumulation of fat in asteroid hyalitis and synchysis scintillans is a locally conditioned precipitate secondary to trauma or hemorrhage. Unilateral fat infiltrates in Coats' disease and the monocular exudative macular retinopathies may also be considered as such although the differentiation is here less clear and more open to question. Such local disturbances will be considered insofar as is necessary to complete the clinical picture of lipid disorders in ophthalmic practice.

Abnormal concentrations of lipids, using this term in its broader inclusive sense as indicated in Table 1, are found in the tissues of individuals having no elevation of this substance in the serum. In such cases the defect is probably in the intracellular enzymatic system, resulting in the improper utilization of the fat provided in normal proportions in the serum. Abnormal concentrations of lipids are also found in the tissues of individuals having an abnormal increase in the lipid content of the serum. When sufficiently elevated this overloading can be detected by the change in the character and color of the blood in the retinal vessels. Deposition of fat in tissues associated with elevated serum lipids results from a breakdown in the normal transportation mechanism by which these substances are moved from storage depots to points of utilization. Table 2, modified from Thannhauser,[2] differentiates the conditions pertinent to this paper into these two basic divisions; that is, those with normal and those with abnormally elevated lipid values.

Tables 1 and 2 will be found useful in orientation as we turn now to an investigation of lipid deposits in ocular tissues in relation to basic systemic disorders. The ocular lesions will be considered in the usual anatomic sequence.

ADNEXA AND ORBIT

Xanthoma may develop in the lids, orbit, and globe of individuals having no elevation of blood lipids. They are encountered more frequently in hypercholesteremic individuals. Clinically these lesions are differentiated into xanthoma planum (xanthelasma)

TABLE 2

DIFFERENTIATION OF CONDITIONS WITH NORMAL AND ABNORMALLY ELEVATED LIPID VALUES

Disease	Predominant Material Deposited	Topography	Histologic Features	Ophthalmologic Signs
1. Nonhyperlipemic				
A. Histiocytosis: (Eosinophilic granuloma, Hand-Schüller-Christian, Letterer-Siwe, and nevoxanthoendothelioma)	Lecithin cholesterol and cholesterol esters	Random isolated or disseminated destructive lesions in bone, connective tissue, serosal surfaces, lymph nodes, skin, etc.	Histiocytic proliferation with or without eosinophil, lipidization may be absent in early lesions, prominent in sclerosed late lesions	Exophthalmos, unilateral or bilateral
B. Niemann-Pick	Sphingomyelin	Universal involvement of reticulo-endothelial system and nervous system	Cytoplasmic deposits in neurons and retinal ganglion cells, reticuloendothelial cells throughout the body	Cherry red spot in macula (60%)
C. Tay-Sachs intermediate forms, Spielmeyer-Vogt	Galactoside	Involvement similar to Niemann-Pick, but less widespread and concentrated particularly in brain and eye. Viscera may not be involved	Cytoplasmic deposits in neurons and retinal ganglion cells	Cherry red macular spot, grey thickened retinal pallor of optic disc
D. Hurler's syndrome	Mucopolysaccharides (chondroitin sulfate and fat)	Universal or widespread involvement of brain, liver, spleen, bone marrow, connective tissue, eye, blood vessels	Cytoplasmic deposits in parenchymatous cells such as neurons, liver cells, and in connective tissue and retino-endothelial cells	Corneal haze, thickened eyelids.
E. Gaucher's	Kerasin containing glucose	Widespread involvement, predominantly of lymph hemopoietic apparatus (spleen, liver, bone marrow, lymph nodes)	Characteristic accumulations in reticuloendothelial cells (Gaucher cells)	Wedge shaped conjunctival thickening, retinal hemorrhage secondary to anemia
2. Hyperlipemic				
A. Hypercholesteremia 1. Idiopathic 2. Secondary a. Biliary cirrhosis	Cholesterol	Blood vessels, connective tissue, skin	Atherosclerosis, xanthomata	Xanthelasma palpebrarum arcus senilis
B. Hyperlipemia	Neutral fat	Blood vessels, connective tissue, skin	Atherosclerosis, xanthomata	Lipemia retinalis

and xanthoma tuberosum including the tendon-sheath xanthoma. Eruptive xanthomas are reversible lesions, generally disseminated, but occasionally involving the lids. These will be considered subsequently.

Xanthelasma (xanthoma planum) are frequently encountered in ophthalmic practice. These lesions, which generally appear in the third and fourth decade, develop symmetrically usually about the inner third of the upper lids. They are only slightly elevated and indurated. In color, they vary from a lemon yellow to a dusky brown. They grow slowly with no interference in function. The lesion consists of an accumulation of lipid material with histiocytes. Excepting the cosmetic blemish they have no local significance. For many years xanthelasma have been associated with coronary insufficiency and although this relationship has not been universally accepted in modern medicine the relationship appears more than coincidental.

Epstein, Rosenman, and Gofman,[8] studying the serum lipoproteins in xanthelasma, found that in 35 patients exhibiting these lesions 47 percent had hypercholesteremia while 20 percent had advanced coronary disease. In discussing this paper Dr. Bart Spence referred to 182 patients from the Mayo Clinic who had xanthelasma (xanthoma of the eyelids alone). Sixty percent of these patients were healthy and had normal blood lipids, 40 percent had elevated blood lipids and cardiovascular disease. In his previous studies, he stated that 50 percent of the patients with xanthelasma alone had some elevation of blood lipids, especially cholesterol, and that 50 percent of those with elevated lipids, or 25 percent of the total, had evidence of cardiovascular disease.

Among the Duke Hospital records were 47 cases of xanthelasma with cholesterol determinations. Of these, 52.3 percent had levels above 250 mg. percent. It would seem that, while the association of xanthelasma with hypercholesteremia is not exact, the presence of these lesions should suggest the possibility of a more widespread disorder, frequently involving the cardiovascular system, and that these lesions present a clinical sign which should require further investigation or at least consideration of the possibility of the more serious disease.

Xanthoma tuberosum, insofar as the scope of this paper is concerned, may be considered as an extension of xanthelasma. The association with atheromatous cardiovascular disease is however much more definite. Deposits are found in the skin of the extensor surfaces of the joints and attached to the tendon sheaths. The lesions may become quite large. Usually in xanthoma tuberosum they are more elevated, more discrete, and of a somewhat darker color than in xanthoma planum. An elevated serum cholesterol occurs frequently in xanthoma planum (xanthelasma) and constantly in xanthoma tuberosum. Histologically the lesions are quite similar consisting essentially of fat-laden histiocytes. The two clinical varieties may occur in the same individual or in different members of the same family. There may be xanthoma planum (xanthelasma) on the lids or the tuberous process may involve these structures. It has been suggested that hypercholesteremia may be determined by a partially dominant gene which gives rise to xanthomatosis when homozygous. In xanthoma tuberosum the viscera are also involved. In such individuals the coronary artery is frequently occluded by atheromatous plaques. The presence of these lesions therefore implies a rather serious prognosis.

The eruptive xanthomas, according to Thannhauser, "are not an entity of a disease but a symptom due to hyperlipemia." The hyperlipemia may be secondary or idiopathic. In the secondary type the foam cells are produced by phagocytosis of lipids which have accumulated through excessive mobilization into the blood of fats and fatty acids. Excessive mobilization of these substances may occur through a variety of unrelated mechanisms as in diabetes where a block in the utilization of carbohydrate prevents the nor-

mally associated metabolism of fat, or, as in nephrosis, where there is an insufficiency of albumin necessary for binding of free fatty acids. The metabolic processes resulting in idiopathic hyperlipemia are not understood. The foam cells found in the primary xanthomatoses which occur in normocholesteremic and hypercholesteremic individuals in contrast to those described in the eruptive xanthomas have been interpreted by Thannhauser to be transformed reticulocytes and histiocytes, fat laden, as a result of aberrations of intracellular metabolism. Dunphy[4] has observed an interesting case of idiopathic hyperlipemia with eruptive xanthoma. The skin lesions varied in intensity in proportion to fluctuations in the lipid levels of the blood. This patient was reported primarily as a case of lipemia retinalis. The lids were not involved and are probably infrequently so in these secondary xanthomas.

Xanthoma disseminatum has been identified by Crocker[5] as including juvenile xanthoma and nevoxanthoendothelioma. Newell[6] has reported two cases of the latter, one of which was associated with lesions of the skin characteristic of xanthoma disseminatum. Newell refers to somewhat similar cases reported by Sanders, Heath, and Maumenee. In these cases there is no elevation of the serum lipids. Nevoxanthoendothelioma may well prove the connecting link, as suggested by Newell, between this disease and those which we have grouped in Table 2 under histiocytosis.

Orbital xanthomatoses with hypercholesteremia but unassociated with any manifestation of systemic disease are occasionally encountered. Orbital xanthomatosis associated with xanthelasma, arcus senilis, and hypercholesteremia is the presumptive diagnosis in the following instance:

CASE REPORT: (M. M. C., E 54465) (fig. 1)

A woman, aged 45 years, presented with painless gradual protrusion of the right eye unassociated with any evidence of disease other than a fasting serum cholesterol of 466 mg. percent, bilateral palpebral xanthoma, and moderate arcus senilis.

Fig. 1 (Anderson, Margolis, and Lynn). Orbital xanthomatosis with xanthelasma, arcus senilis, and hypercholesteremia.

Repeated cholesterol determinations indicated an average reading of around 500 mg. percent. There was a right exophthalmos of six mm., the right eye being displaced slightly downward but not laterally. There was slight limitation of upward motion, no mass could be palpated. X-ray studies were negative as was the examination of the sinuses and upper respiratory passages. There was no indication of involvement of any of the blood vessels. There was nothing in the history or examination to suggest that the exophthalmos might be the result of a metastatic lesion. The absence of skull changes demonstrated by X-ray films and the elevated cholesterol would seem to exclude Hand-Schüller-Christian disease. The age of the patient would also make this unlikely. On the basis of exclusion of other likely causes and the indications presented by the cholesteremia, xanthoma, and arcus senilis, the exophthalmos has been tentatively attributed to an orbital xanthoma. This woman has been under observation for eight months. On a low fat diet there has been no increase in the exophthalmos.

Clinically xanthomatosis of the orbit as illustrated in this case differs from the histiocytosis complex in which are included eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe disease and possibly nevoxanthoendothelioma, in that in the latter the blood lipids are within normal range.

Eosinophilic granuloma, the Hand-Schüller-Christian syndrome, and the Letterer-Siwe disease are now considered as probably different stages of a single underlying disorder of the reticuloendothelial system characterized by the intracellular deposit within reticuloendothelial cells of excessive deposits of lipid substances. Such a disorder is of interest to ophthalmologists because

exophthalmos, usually at first unilateral, may be the first sign. Eosinophilic granuloma of bone is usually an isolated osteolytic granulomatous lesion of the skull with eosinophilic leukocytes predominating in the early stages. Later vacuolated foam cells are more characteristic. Finally healing occurs by fibroplastic proliferation. Hand-Schüller-Christian disease is usually more widespread as will be shown in the case to be reported subsequently. Usually even with extensive involvement, the prognosis is good as the disease is self-limiting, the isolated lesions responding to X-ray therapy. Occasionally, as demonstrated in the following case report, the clinical picture evolves into the more serious Hand-Schüller-Christian type:

CASE REPORT: (R. W., E 03187)

A Caucasian girl, aged two years, was admitted with complaint of swelling in the left temporal area for five months (fig. 2). Examination revealed left ptosis and exophthalmos with a nontender mass approximately four cm. in diameter between the external canthus of the left eye and ear. X-ray studies demonstrated an osteolytic lesion of the left zygomatic bone. A biopsy of the mass demonstrated characteristic histologic features of an eosinophilic granuloma (color plate E). The reaction was composed of a heavy infiltrate of histiocytes and of eosinophilic leukocytes, with a large central zone of necrosis. Although the cytoplasm of the histiocytes was abundant and many were multinucleated, no vacuolar changes suggestive of lipidization were observed. No material was available for lipid stains.

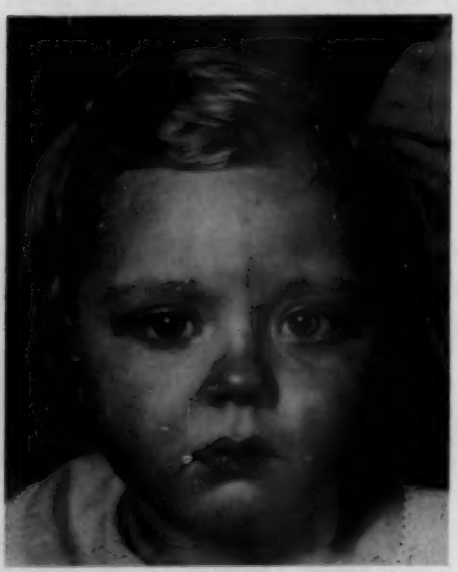


Fig. 2 (Anderson, Margolis, and Lynn). Left exophthalmos, with swelling over the zygoma (eosinophilic granuloma).

Under X-ray therapy there was regression of the osteolytic skull lesion and of a similar process discovered in the left humerus. One year later there appeared widespread punched-out osteolytic areas in both skull and leg bones. The lesions were again treated with marked improvement. Some two years after the appearance of the left temporal mass polydipsia and polyuria were noted. No elevation of blood cholesterol was demonstrated. With the obvious pituitary involvement it was felt that this disease had evolved into the more widespread Schüller-Christian variant of the reticuloendothelioses.

This case is presented as showing the transition from the relatively benign solitary bone lesion to the more widespread progressive osteolytic process with involvement of the pituitary and the secondary manifestation attributable to such involvement.

Hand-Schüller-Christian disease occurs predominantly in children. Only rarely does this condition appear in adult life. However, as illustrated in the following case, this diagnosis cannot be excluded on the basis of age alone.

CASE REPORT: (W. K. D.) (fig. 3)

A 62-year-old man complained of excessive lacrimation with photophobia. Within three months the conjunctiva became chemotic, protruding through the closed lids. There was moderate bilateral exophthalmos, the right eye being two mm. more prominent than the left (fig. 3-a). X-ray films showed no abnormality of the skull. Except for an enlarged heart physical signs and laboratory procedures were noncontributory.

After observation for some months during which the exophthalmos became more prominent the right orbit was explored. This was found to be packed with xanthomatous material. X-ray therapy was applied to the orbits. Although the patient complained less of photophobia and lacrimation, the effect of therapy on the degree of exophthalmos was not impressive.

Except for the enlarged heart, physical findings remained within normal limits although it was obvious that the patient's general condition was deteriorating. Some eight months after the first

severity of the reticuloendotheliosis decreases histiocytes exhibited erythrophagocytic ac-

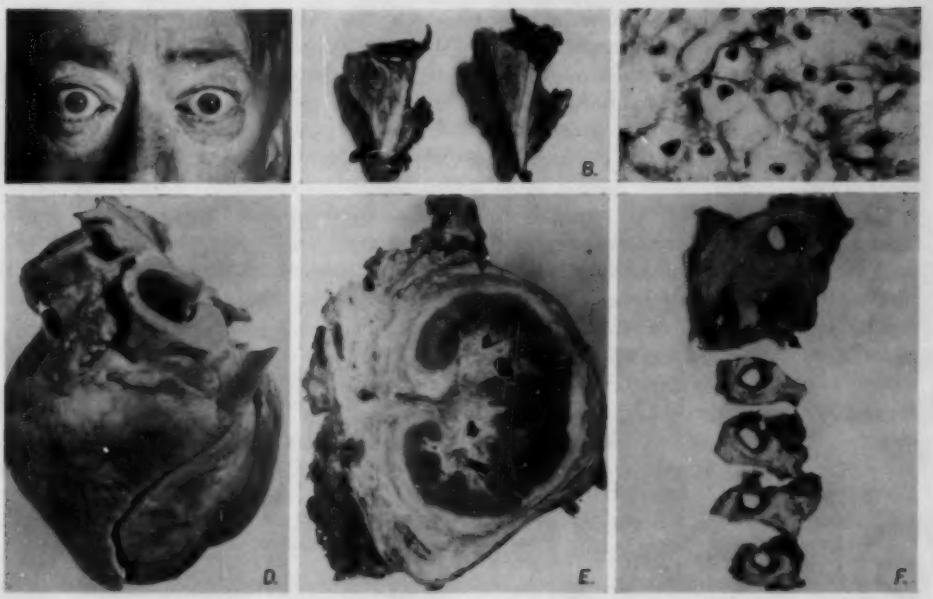


Fig. 3 (Anderson, Margolis, and Lynn). W. K. B. (2380). Lipid reticuloendotheliosis (Hand-Schüller-Christian syndrome), slowly progressive. (A) Exophthalmos without skull involvement or diabetes insipidus. (B) Xanthomatous deposits in orbits infiltrating neither nerve nor muscle. (C) Orbital tissue with typical foam cells. (D) Xanthomatous deposits involving the heart, (E) kidney, (F) aorta.

complaint, bilateral pleurisy developed, weight loss became more rapid. One year after the onset he died following a hemiplegic attack with convulsions. Death was thought to be due to a cerebral infarct and probably not directly associated with xanthomatous deposits. At no time was there polyuria or hypercholesterolemia.

The gross features of this case emphasized the collagenized and lipidized lesions characteristic of chronic Hand-Schüller-Christian disease in the adult. Of particular interest for this paper was the massive involvement of both orbits by the process, producing severe exophthalmos, yet sparing the optic nerve and extraocular muscles (fig. 3-b). Thick sheaths of sclerotic tissue irregularly streaked with yellow fatty zones encased the aorta (fig. 3-f), heart (fig. 3-d), kidneys (fig. 3-e), adrenals, pleura, vertebral column, and infiltrated the dura and auricular endocardium. Focal yellow sclerotic lesions were present also in the vertebral bodies. Multiple cerebral infarcts, unrelated to the primary disease process, were present.

Although the bulk of the infiltrating masses were composed of dense collagenous tissue typical of the end-stages of the process, varying degrees of activity were evident at a microscopic level. This active phase was manifest in small scattered foci of histiocytes which were frequently multinucleated and had a homogeneous amphophilic cytoplasm with fibrillary processes. Eosinophilic leukocytes were exceedingly sparsely scattered in such foci. In all active zones a transition of the histiocytes to characteristic foam cells was observed. This transition was manifested as a progressive accumulation of cytoplasmic vacuoles, beginning in the marginal regions of the cell bodies, associated with a retraction of processes and a shrinkage and condensation of the nuclei. The late stage of complete lipidization is illustrated in Figure 3-c. Although many of the histiocytes were small and elongated, a clear transition toward the collagenous tissue was not recognized.

This case supports the contention that the

as eosinophilic granuloma, Letterer-Siwe ... ties of the histiocyte, rather than as a pri-

severity of the reticuloendotheliosis decreases with age. Furthermore, it demonstrates that the disease may be quite extensive without X-ray manifestations, without diabetes insipidus, and that wide-spread involvement may develop without seriously impairing function.

The other extreme of this type of xanthomatosis is the Letterer-Siwe disease. In addition to the skeletal involvement the viscera are affected. The disease is usually rapidly fatal. Ocular involvement is infrequent. Perhaps as indicated by the following report the ocular structures are affected more frequently than indicated by the ophthalmoscope.

CASE REPORT: (J. M. T., D 9344).

A 16-month-old infant presented with lassitude and weakness and was found to have a marked secondary anemia and an osteolytic defect over the right frontotemporal area and an enlarged liver. Bone-marrow smears were loaded with large reticuloendothelial cells which compared with those seen in diseases of abnormal cellular metabolism of lipid. There was no elevation of serum lipids. Biopsy of the skull lesion was interpreted as compatible with Hand-Schüller-Christian disease.

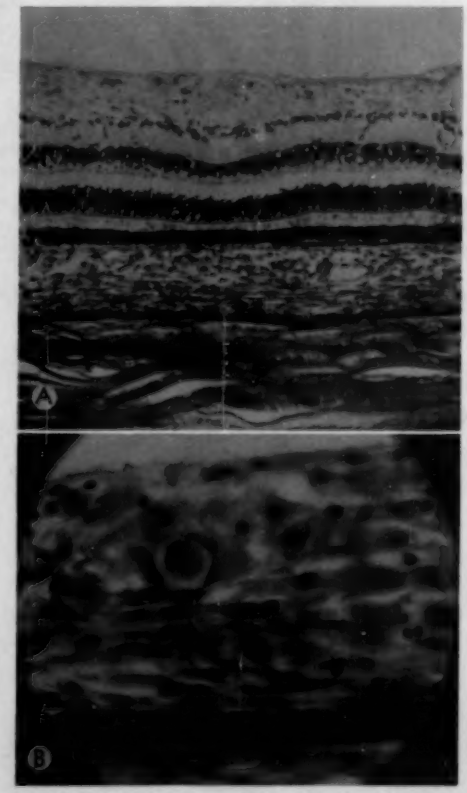
The child was under observation for three months. During this period her condition steadily deteriorated, the anemia becoming more pronounced in spite of all supportive measures. The cholesterol level remained within normal levels. She died shortly after the last admission for a persistent nose bleed, hemoglobin having been reduced to 1.5 gm., the red blood cells being recorded as 0.9 million.

As the child was observed and the record reviewed, the possibility of Letterer-Siwe disease was considered since there was obvious visceral involvement. Autopsy findings support such a conclusion. The ocular system did not appear clinically to be involved in the disease process. Ophthalmoscopic examination was reported as negative. However, a routine section of the eye disclosed an infiltrate of histiocytes in the posterior choroid.

This case, which was clinically characteristic of Letterer-Siwe disease, presented at autopsy a widespread histiocytosis involving bone marrow, lymph nodes, spleen, thymus, dura, heart, lungs, liver, skin, and connective tissues at many other sites. The bone lesions were both diffuse infiltrates and focal zones of destruction. There were widespread petechial hemorrhages, and the proliferating histiocytes exhibited erythrophagocytic activity, with resultant abundant accumulations of hemosiderin in their cytoplasm. No eosinophilia was observed in the lesions. In the infiltrates there was a variable but sometimes advanced degree of lipidization of the histiocytes accompanied by early fibrosis of the involved tissues. In the eye the sole manifestation of the process was the presence of an infiltration of histiocytes in the posterior region of the choroid (figs. 4A and 4B, color plate F).

THE UNIFIED CONCEPT OF THE HISTIOCYTOSES

There is an extensive literature supporting the concept that the conditions designated



Figs. 4A and 4B (Anderson, Margolis, and Lynn). S. M. T. (D-9344). Infiltration of histiocytes in choroid. Letterer-Siwe disease.

Descemet's membrane, the latter being most

require a transplant. In the removed host

as eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease are "closely related expressions of a single nosologic entity."[7] Evidence supporting this idea is best summarized in a critical review by Lichtenstein.[7]

The difficulty in the analysis of this relationship has stemmed from the fact that information on these pathologic processes has been obtained largely from limited studies of individual cases; for example, from surgical biopsy material in the early phases of eosinophilic granuloma and from autopsy studies in Hand-Schüller-Christian disease. Further, this interrelationship has been obscured by the varied clinical manifestations of these diseases, ranging from the frequently self-limiting character of the eosinophilic granuloma, through the slowly progressive but benign course of Hand-Schüller-Christian disease, and to the usually malignant progression of Letter-Siwe disease. However, a strong chain of evidence linking these processes together has been constructed from serial biopsy studies, following cases through their clinical course and by autopsy studies in those cases terminating fatally. The frequently recorded progression of a single case through clinical and histopathologic manifestations characteristic of two or of all three of these entities provided a cogent argument supporting an integrated concept of these processes. The cases cited in the present communication corroborate this view.

If the unified concept of these entities is accepted, it is necessary to question their place among the disorder of lipid metabolism. Lichtenstein has stated that the fundamental nature of this process is that of a proliferative histiocytosis, possibly inflammatory, with or without an accompanying eosinophilic reaction, which at its outset exhibits no tendency toward lipidization. He insists that the xanthomatous stage seen at autopsy in the classical case of Schüller-Christian disease has focused undue attention on this aspect of the lesion. This phase is regarded by him as a secondary lipidization, an expression of the phagocytic properties of the histiocyte, rather than as a primary metabolic disorder of the reticulum cell resulting in intracellular lipid accumulation, as conceived by Thannhauser.[8]

The absence of elevated serum lipids in the histiocytic processes offers a further argument against these entities being a primary disorder of lipid metabolism. On the other hand the xanthomatous end-stage achieved by virtually all of the chronic proliferative lesions is strongly suggestive of a specific primary progressive process. However, the random, rather than predictable, localization of the lesions argues against a systemic metabolic disorder.

At present the nature of the stimulus provocative of the histiocytic proliferation is unknown. The fact that the earliest recognizable lesions are expressed as circumscribed foci of tissue destruction, crowded with histiocytes and eosinophils, *in the absence of demonstrable lipids,* makes it most difficult to conceive of this process as a primary disorder of fat metabolism. While the xanthoma representing the end-state of this reaction may bear comparison to the xanthoma of the hyperlipemic states, it appears that different pathogenetic mechanisms are involved. Further studies of the chemical composition of these xanthomatous lesions and a comparison with the similar lipid deposits about chronic inflammatory foci of known etiology are badly needed.

Cornea

The experimental production of arcus lipidis in hypercholesteremic rabbits has revived interest in this lesion as it occurs in man. Cogan and Kuwabara[9] have investigated this phenomenon and shown that the fat deposit so produced is quite different from the arcus senilis in man. It is the opinion of these investigators that in the human such a lesion is only occasionally associated with hypercholesteremia and atherosclerosis. In man, the sudanophilic droplets occur extracellularly in between the collagenous laminae of the stroma and there is a diffuse sudanophilia of both Bowman's and

Descemet's membrane, the latter being most extensively involved. This differs from the experimental lesion which was produced in vitro by the injection of sodium oleate directly into the cornea. They were able, however, to produce the extracellular sudanophilia as seen in arcus senilis in rabbits by the injection of hypercholesteremic plasma into the cornea of rabbits. Their conclusion was that the fat seen in arcus senilis was probably not the result of active lipogenesis by the cornea but a deposition of blood fat into the extracellular spaces of the cornea.

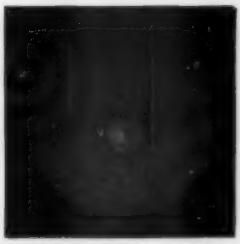
Forsius[10] determined the serum lipid values of 165 individuals of assorted ages and correlated these findings with degree of arcus senilis and with age. He found that the cholesterol concentration in those of this group between 20 and 49 years of age was 44 percent higher than for those without arcus. There was a parallel between the degree of arcus and the serum cholesterol and phospholipid values in this age group; the more intense the arcus the higher these values. He concluded that the development of an arcus lipidis in an individual of less than 50 years of age was evidence of extensive lipido-chemical alteration in serum. On the other hand, arcus in the older age group was not as a rule dependent on disturbed fat metabolism but related to local senile changes in the cornea. These studies strongly indicate that the appearance of the arcus in a young individual merits at least the consideration of the possibility of an underlying disturbance of lipid metabolism and possibly further investigation of systemic vascular disease implied by its presence.

Diffuse infiltration of the cornea with lipidlike substances is occasionally seen as a primary dystrophy. Here also there may be an associated cholesterolemia although the association is probably coincidental. In the Duke Clinic one such case has been studied histologically by Davidson.[11] In this case both eyes were involved, one so extensively as to require a transplant. In the removed host button the epithelium, Bowman's and Descemet's membranes, as well as the endothelium, were free of fat. Large and small globules of fat were numerous within macrophages localized about invading vessels and more extensively spread in the extracellular lamellae, particularly the anterior two thirds. Late neovascularization and signs of irritation differentiate primary lipid dystrophy of the cornea from another disease in which there is likewise diffuse corneal infiltration, the so-called lipochondrodystrophy, also known as Hurler's disease.

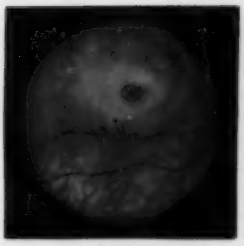
In lipochondrodystrophy the gargoyle skull with grossly thickened repulsive features, drooling mouth, joined on a dwarfish trunk by a short thick neck, the protuberant abdomen with the umbilical and inguinal hernia associated with hepatosplenomegaly are characteristic. These features which are so remarkably similar in all instances easily establish the diagnosis. Regardless of race or color they appear to have been stamped from the same stenotype (fig. 5). However, more and more cases of a form frusté are recognized in adults. Two such have recently been studied post mortem in the Duke Clinic.

Seventy-five percent of these cases are said to have corneal opacities. The corneal glaze or ground glass appearance (figs 6A and 6B) is due to a fine grayish punctate lesion deep in the stroma. The microscopic interpretation of these will be discussed later. Hogan and Cordes[12] concluded, after studying the corneas of three of these individuals and after reviewing the case reports of Berlin and Rochat, that the corneal changes were caused by the infiltration of numerous large phagocytic cells into the region of Bowman's membrane. Most of these phagocytes and the corneal corpuscles showed numerous fine granules in the cytoplasm. These were present in frozen section but were removed by fat solvents, "an indication of their possible lipid nature. The

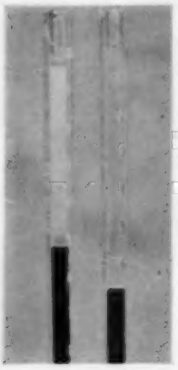
Color Plate I (Anderson, Margolis, and Lynn). Ocular lesions related to disturbances in fat metabolism.



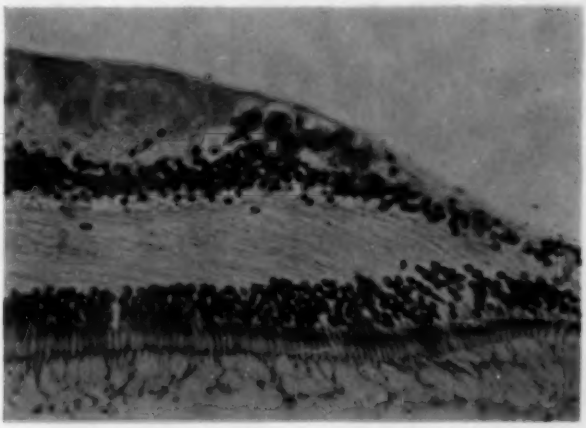
A. *Lipemia retinalis in diabetes.* Arteries and veins engorged, color varying from salmon to cream due to increase in neutral fat content of blood.



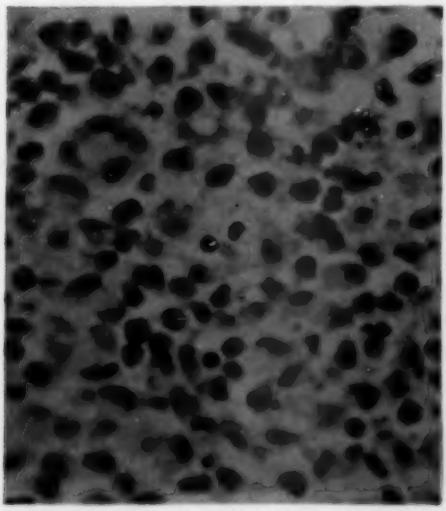
C. *Tay-Sach's disease.* Snow-bank ring, central crater framing cherry red spot.



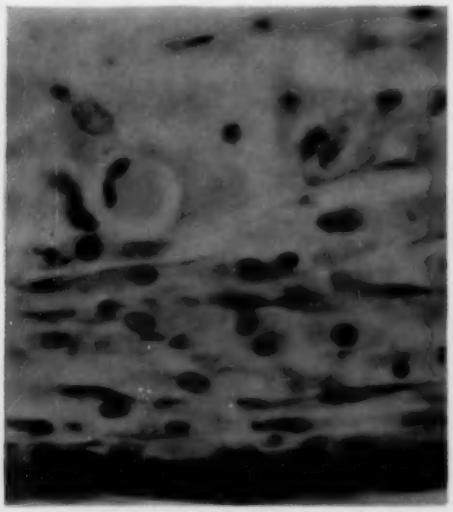
B. Opalescent character of blood shown in contrast to normal blood sample (right tube). Volumetric fat, 528 mm.



D. PAS preparation of macular area in Figure C, indicating cyclolipid and glycoprotein in degenerating ganglion cells.



E. *Eosinophilic granuloma.* Infiltrate of histiocytes and eosinophilic leukocytes.



F. *Letterer-Siwe's disease.* Histiocytic infiltration in posterior choroid.

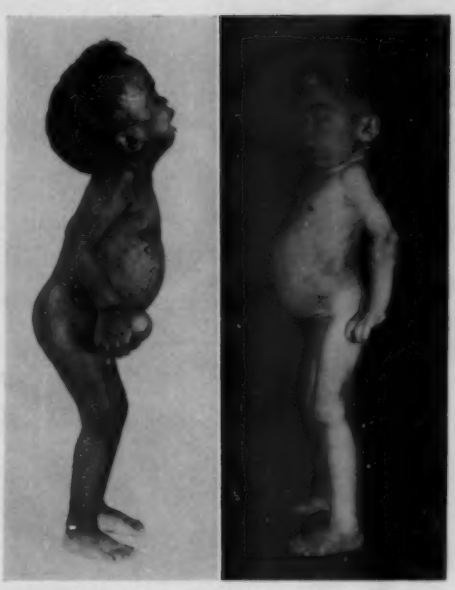
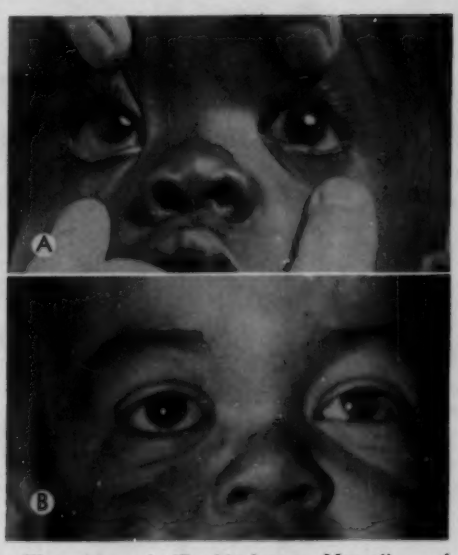


Fig. 5 (Anderson, Margolis, and Lynn). (Left) J. D. (D-93807). (Right) G. C. (C-35064). Lipochondrodystrophy (Hurler's disease).



Figs. 6A and 6B (Anderson, Margolis, and Lynn). (A) J. D. (D-93807). (B) G. C. (C-35064). Corneal infiltrates in lipochondrodystrophy (Hurler's disease).

granules however do not take the usual stain for fat." More recently these deposits have been shown to contain, along with some fat, an abnormal mucopolysaccharide, a chondroitin sulfate. This material is also present in the urine in large amounts. There is as yet no general agreement and until the true nature of the underlying biochemical process is understood retention of the present designation of lipochondrodystrophy will avoid confusion.

One of our cases has been studied post mortem (fig. 5-b). This case presented classical pathologic anatomic features of the syndrome. Virtually everywhere in the central nervous system neurones were greatly ballooned by cytoplasmic deposits which were highly soluble in all fixatives. The liver was greatly enlarged as the result of similar accumulation in the parenchymal cells. The spleen and lymph nodes and bone marrow were crowded with great numbers of histiocytes with a foamy distended cytoplasm. A striking endothelial thickening of the aorta and its major branches had resulted from the proliferation of fibroblasticlike cells similarly laden with the abnormal metabolite. In the eye the laminae of the cornea were slightly separated by a vacuolar cytoplasmic swelling of the stromal cells (fig. 7). At the periphery of the cornea there was an extension of foamy histiocytes between Bowman's membrane and the epithelium. Slight vacuolar changes and ballooning of the retinal ganglion cells were also present. The eye was not subjected to fat stains. Elsewhere the cytoplasmic accumulations were very weakly sudanophilic, and faintly reactive with the periodic acid-Schiff method. An unusual feature was the enlargement and vacuolar alteration of hepatic Kupffer cells and accumulations of foamy macrophages in Virchow-Robins spaces in the central nervous system; both of these reticuloendothelial components were strongly sudanophilic.

Comment

Our understanding of the fundamental nature of Hurler's disease has been consider-

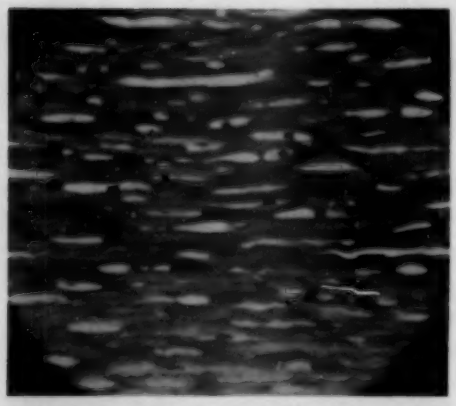


Fig. 7 (Anderson, Margolis, and Lynn). G. C. (C-35064). Vacuolar cytoplasmic swelling of corneal stromal cells in lipochondrodystrophy.

ably clarified by recent studies with the demonstration of mucopolysaccharides both as storage products and as urinary excretory products. McKusick[13] has called attention to the skeletal and connective-tissue changes in the disease and has classified it among the "heritable disorders of connective tissue." However, the generalized storage of the abnormal metabolic products in neurons, parenchymatous cells of the liver, and throughout the reticuloendothelial system, such as illustrated in this case, emphasizes the inadequacy of this limited concept of the disease. McKusick has, however, given us a careful clinical description of the disease and has called attention to the presence of less severe manifestations observed in the adult. The differential diagnosis of corneal lesions in the latter group may pose some problems if the clinical features of the disease are not overt.

Lens

Other than the crystalloid formation occasionally observed in diabetic cataracts we have never observed a lesion which was suggestive of lenticular lipidosis. Lipids are said to be slightly increased in some forms of cataract. The degree of this increase and its significance in relation to the lens changes is controversial. Xanthomatosis lentis has been reported,[14] as has cholesterinosis lentis.[15]

Vitreous

The vitreous is singularly inert in the presence of systemic metabolic disturbance. Local conditions, usually an old choroiditis, contusion or hemorrhage, occasionally produce monocular precipitates (synchysis scintillans) which have been identified as cholesterol crystals. In the degenerated and fluid vitreous these may find their way into the anterior chamber producing the unusual picture in which the pupil becomes obscured by a glittering golden wave as the eye is moved. The individual crystals move at random in synchysis, gradually settling into a conglomerate mass as the eye comes to rest. This unrestricted movement differentiates this condition from the more common asteroid hyalitis in which the formed elements of protein residue, forming as the vitreous changes from a jelly to a solution, retain a definite pattern, are globoid in shape, and move en masse as the eyes are turned, each element maintaining its position with relation to the other opacities and returning to the same position in the ophthalmoscopic field. These latter opacities are thought to be calcium soaps of fatty acids.

Retina

Lipemia retinalis designates a retinopathy characterized by changes in the color and caliber of both retinal arteries and veins. The normal contrast between the darker larger vein and the smaller redder artery is lost as both, depending on the degree of saturation of the blood column with neutral fat, vary from a salmon pink to a yellow cream in color. As the fat content increases the retinal vessels become more engorged until they stand out like Neoprene casts in bold relief (fig. 8). Perceptible shift in color values of the retinal vessels becomes apparent when the saturation of the blood reaches three to four percent of neutral fat. As the fat con-

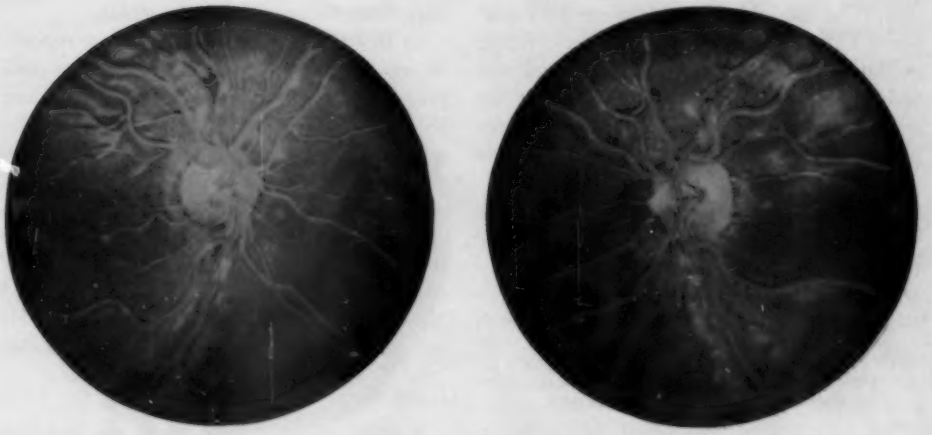


Fig. 8 (Anderson, Margolis, and Lynn). J. M. (B-56856). Lipemia retinalis (diabetes).

tent rises the blood column changes toward a cream color. A case has been observed in which both retinal arteries and veins were quite white.

The discovery of a lipemia retinalis in an unconscious patient may establish a presumptive diagnosis of diabetic coma. Lipemia retinalis occurs infrequently in other conditions.

In 78 reported cases 65 were in diabetes.[18] In the 13 remaining there was no evidence, clinical or laboratory, of this disease. The condition has been seen in lipid nephrosis, starvation, and in idiopathic or essential hypercholesteremia.

The serum becomes milky solely as the result of the increase in neutral fat. Increase in cholesterol or phospholipids does not cause opalescence. Possibly other factors such as a relative decrease in the phospholipids which hold the other lipids in colloidal solution may be the critical factor producing the condition. In six cases personally observed all have been young diabetics.

The photographs of retina and blood sample are typical of the diabetic type (fig. 8 and color plate A and B). The opalescent character of the serum is shown by comparison with normal serum in the accompanying tube.

In this instance a 29-year-old man had noted polyuria, polydipsia, and weakness for one month. There had been drowsiness and loss of appetite for 48 hours. The retinal vessels were distended, gave the appearance of rigidity, quite in contrast to the relaxed sacculation seen in older diabetics, and stood out in the retina in sharp sculptured relief. Both arteries and veins were similar in color, varying from a dusky rose at the disc through a salmon pink to a cream tone in the periphery. In the distended veins one could easily see large particulate oleaginous yellowish bodies of irregular contour being swept along in the venous blood and cascading over the disc edge into the cup. With slight pressure on the globe the venous circulation could be retarded or stopped. By this maneuver one obtained what simulated a stroboscopic effect in which these particles, some being almost the diameter of the vessel, as they slowed, stopped, and bobbed about with limited excursion, could be studied more carefully. They were not of uniform size. They were definitely not globular. The surfaces were pitted and vacuolated, resembling freshly churned butter particles. Spontaneous pulsation was not observed in either artery or vein.

The blood cholesterol was 1,215 mg. per-

cent. The total blood lipids were 17.1 gm. percent in the serum, the volumetric fat in millimeters was 528. The lipemia retinalis had completely disappeared 72 hours after admission although the cholesterol was reported as 1,135 and the volumetric fat as 255.

In the case described the fatty particles were in some cases almost equal in diameter to the larger veins. It is interesting to speculate on the mechanism by which such particles passed through a capillary bed of much smaller diameter.

Retina-neuronal lipidoses

The retina is involved in lipidoses which are purely neuronal in distribution and in lipidoses in which there is also visceral involvement. Two diseases which are typical of such distribution are those of Tay-Sachs and Niemann-Pick. The cherry red macular spot is the principal distinguishing feature of Tay-Sachs disease. Sixty percent of the Niemann-Pick cases are also said to present a cherry red macular spot along with visceral involvement. While these two conditions can be differentiated by chemical analysis of neural tissue clinical differentiation is in fact usually made on the basis of visceral involvement in Niemann-Pick.

Tay-Sachs disease is generally considered as the infantile form of a larger group of amaurotic idiocy or cerebromacular degeneration. The usual division is as follows:

1. Infantile amaurotic idiocy (Tay-Sachs)
2. Late infantile form (Bielschowsky)
3. Juvenile amaurotic idiocy (Spielmeyer-Vogt
4. Late juvenile form (Kufs)

Other less clearly differentiated conditions characterized by retinal and cerebral changes have been described by Refsum, Kufs, and Batten-Mayou.

The ophthalmologist will be interested primarily in the Tay-Sachs, Spielmeyer-Vogt, and Niemann-Pick groups since in these conditions the ophthalmic signs are such important factors in the diagnosis.

In this paper we present two case reports in which the cherry red macular spot was present. The first is unique in that we are able to correlate the histopathology of the macula with an acceptable fundus photograph taken before death. The second report records the appearance of cherry red macular spots in a 17-year-old girl. So far as we can determine these spots have previously only been reported in Tay-Sachs and Niemann-Pick diseases, in which the survival period does not extend beyond childhood.

Case report: (P. A. T., E 13500)

A white girl, aged three years, who had been born prematurely, with a birth weight of five lb., had developed slowly. Because of retarded development the eyes were examined at six months of age and no abnormality of the macula was noted. At one year of age she sat and crawled. From this age progressive physical and mental deterioration were apparent.

The fundi were re-examined. The discs were slightly pale but probably not more so than is usual in an infant in this age group. The blood vessels appeared normal. In the central retina of each eye the normal orange red reflex merged gradually into a glistening white fluffy, elevated snowbanklike ring, the rolled inner edge of which sloped sharply toward the fovea creating a craterlike setting in the center of which was framed the cherry red spot characteristic of Tay-Sachs disease (fig. 9 and color plate C).

As the deterioration progressed convulsions were observed. These occurred with increasing frequency. It is of interest that the parents reported that vision did not appear to have been affected although nystagmoid movements were noted.

The child died at the age of three years from an aspiration bronchopneumonia. At autopsy the brain was observed to be pale waxy in color and to have a denser than normal consistency. The convolutional pattern was normal but flattened. Cut surfaces showed no normal demarcation between white and gray matter. Marked destruction of neurons was observed in the cerebrum, cerebellum, and brain stem as the result of accumulated lipoid substance.

The eye from this case (Surg. Path. A 17022) was studied through the courtesy of Dr. R. Hardee, Rex Hospital, Raleigh, North Carolina. The pathologic features in the eye were confined essentially to the ganglion cell layer of the retina. Here there was a striking paucity of cells, and the remaining ganglion cells were remarkably enlarged by a ballooning of the cytoplasm. Although the central zones of the retina were most severely affected, the degenerative changes extended to the peripheral zones. In the hematoxylin-eosin stains the cyto-

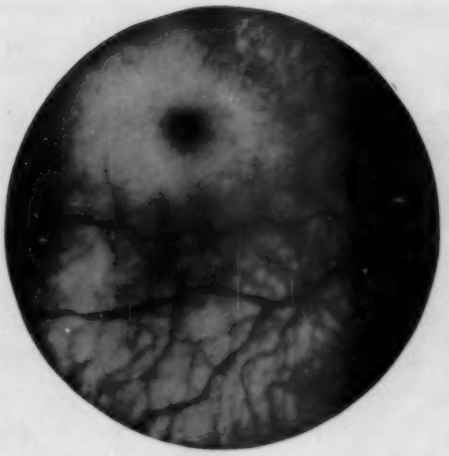


Fig. 9 (Anderson, Margolis, and Lynn). P. T. (E-13500). Cherry red macular spot. Tay-Sachs disease.

plasm appeared empty except for a finely reticular pattern. With the use of the periodic acid-Schiff reaction,[28] the general indicator for carbohydrates of the clycolipid and glycoprotein class, the ganglion cells gave a varying response, from negative, to weakly positive, to strongly reactive. A similar variability in intensity of staining was observed with Luxol fast blue, a phospholipid indicator,[27, 28] but almost all ganglion cells were stained. When these two stains were used in combination,[29] the ganglion cells reacted with one or the other of these dyes. Many of the most intensely reacting cells had an irregularly shaped, pyknotic nucleus. It is possible that some of these were phagocytes, as suggested by Greenfield[29] who reported similar periodic acid-Schiff reactions in the retinal ganglion cells in lipidosis.

Case report: (T. R., D 23753)

A white girl, aged 17 years, was admitted for investigation of "jerking spells" for four years. These spells chiefly involved the legs and arms. There was some difficulty in stair climbing. Occasionally there was difficulty in writing.

Neurologically the picture was far from clear. There were sporadic rapid movements of the arms and legs. These were not athetoid and appeared to some extent at least to be volitional. Cerebellar tests were performed with rapid coarse intentional tremor. All reflexes were bilaterally hyperactive.

Typical cherry red spots were present in each macula (fig. 10). Although the patient had complained of visual difficulty, the acuity uncorrected was at least 20/50. Refraction was not recorded. The peripheral and central fields were normal. But for the presence of the macular lesions this patient would have been classified as a neurosis.

Following the discovery of the cherry red macular spots the patient was further investigated. The electroencephalogram showed generalized abnormal activity with mixed fast and slow waves. Laboratory studies were otherwise noncontributory.

An older bedridden sister has had similar complaints since the age of 19 years. This sister's fundi were also observed to contain cherry red macular spots. Her neurologic signs were more advanced than those of the patient. This case was classified by the neurologists as a cerebromacular degeneration, possibly of the Spielmeyer-Vogt type.

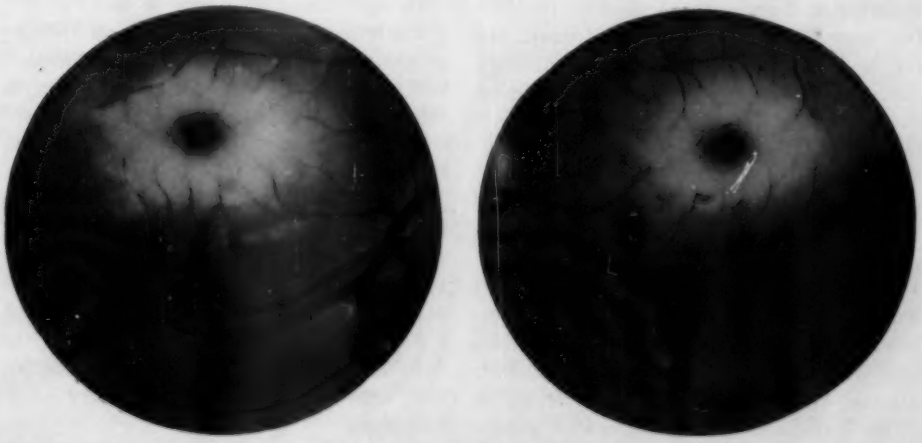


Fig. 10 (Anderson, Margolis, and Lynn). T. R. (D-23753). Cherry red macular spots in 17-year-old girl. Vision, 20/50; indefinite neurologic signs; undiagnosed.

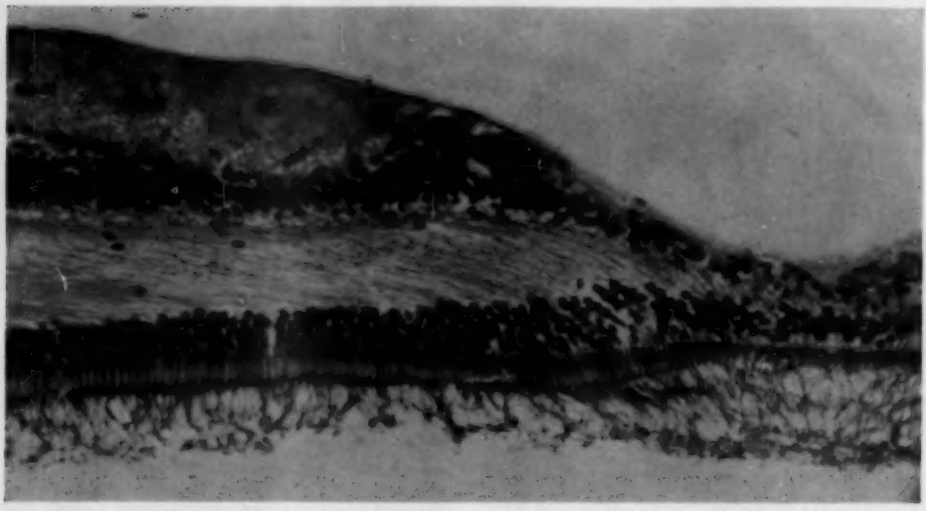


Fig. 11 (Anderson, Margolis, and Lynn). Macula in Tay-Sachs disease. Note ballooning and degeneration of ganglion cells.

COMMENT

On the basis of the information available the disease in these two sisters whose symptoms began at maturity cannot be more clearly classified than as a type of cerebromacular degeneration. The unusual feature is the appearance of the cherry red macular spots at such a late age. So far as we can learn these spots have not been previously reported in degenerative lesions of the central nervous system in this age group. On the basis of the ophthalmoscopic findings one would question the diagnosis of juvenile familial idiocy. The macular lesions in Spielmeyer-Vogt disease are not sharply circumscribed or elevated. There is no white halo as seen in this case. Usually there is a brick red splotch with irregular borders which may be located somewhat eccentric to the fovea. As shown in this case a vision of at least 20/50 is possible in such affected retinas. Cherry red spots appear in more than half of the case reports of Niemann-Pick disease. While chemical analysis of brains of the Tay-Sachs and Niemann-Pick groups indicate somewhat different metabolic processes, and even though there is evidence that Tay-Sachs disease is not a primary lipidosis, the two have many clinical similarities. Genetic proof of this close relationship is the appearance of these separate diseases in siblings.[21] The appearance of the cherry red spot in both, and with the exceptions noted above (in no other disease), also indicates a close association.

In ophthalmic literature there is a persistently recurring suggestion that the degenerative macular lesions, both pigmentary and exudative, especially when occurring in elderly individuals, are secondary to atheromatous changes in the retinal and choroidal circulation.

While this theory is very attractive in its simplicity it is far from proven. There is no clear proof that these changes occur as a result of the atherosclerotic process with resultant circulatory failure. The lipid deposits encountered in these lesions may be quite impressive, as in retinitis circinata, but such are in all probability secondary manifestations.

On the other hand one occasionally ob-

serves the typical circinate retinopathy develop within a few weeks after the eye has regained a high functional state following cataract extraction. It might be reasoned that such lipid deposits resulted from a relative anoxemia developing in an area in which the metabolic processes previously dormant have been accelerated with return of function.

We have observed two instances in elderly atherosclerotic women where a developing retinitis circinata drastically reduced a previously satisfactory result. In one of these the deposits, which from their appearance are assumed to be of a lipid nature, have disappeared with return of satisfactory vision.

Of whatever origin there seems little question but that excessive lipids are deposited in the retina, that they have a predilection for the macular area, and that their presence there interferes with function. While the resorption of such deposits seldom results in improvement of vision their prevention may well serve to conserve sight. Any therapeutic modality effective in such control would be most helpful.

In the retina subendothelial atheromatous plaques are found well out in the arteriolar tree and even in the veins, at least in the veins at the arteriovenous crossing. The genesis and evolution of these plaques may well be basis for some of the retinopathies whose pathogenesis is at present obscure. When detected and properly interpreted they may also afford considerable insight into the general circulatory condition, somewhat as the arteriolar changes in hypertension are indicative of the degree of the hypertensive disease. In our aging population such recognition is of great importance in relation to dietary regulation which might retard or prevent the development of atheroma.

The atheromatous process is beyond doubt associated with hypercholesteremia. While this association is not obligatory, there seems sufficient statistical evidence to justify this concept which at least has the virtue of offering some hope for a therapeutic approach to the problem. Whether the subendothelial atheromatous plaque develops solely as a result of hypercholesteremia or as the result of this increasing difficulty of an aging organism to utilize such fat, or whether these plaques originate as a result of fibrinous deposits (Rokitanski) is still undecided. Of whatever origin, the lipid nature of the deposit is unquestioned.

Therapy

The therapeutic approaches to these diseases can be discussed briefly. With the exception of X-ray therapy for the isolated lesions of the Hand-Schüller-Christian type, the normocholesterolemic diseases have no definitive treatment. However, those diseases associated with abnormal amounts of fat in the blood are at least partially amenable to various therapeutic approaches. If the abnormal blood fat is secondary to other diseases such as diabetes, nephrosis, cirrhosis, and myxedema, then treatment of the primary lesion often produces striking results. For example, the alleviation of myxedema often relieves angina and further reduces the likelihood of subsequent coronary disease, and insulin in untreated diabetes promptly causes removal of the elevated blood fat, with clearing of lipemic retinalis.

The idiopathic hyperlipemias are also amenable to treatment. Until recently these states have been approached from the viewpoint that hyperlipemia represented a lessened ability of the blood to transport these lipids. Treatment thus was aimed at lightening the load on this transport system by removing one source of blood fat, that is the dietary fat, and indeed such low fat diets—for example, the rice diet of Kempner—have been effective in lowering blood fat levels and causing the disappearance of xanthomata and the absorption of fatty deposits in the retina.

Currently, similar results of lowering blood lipids and dissolving xanthomata by

changing the type of fat in the diet have been obtained. Bronte-Stewart, Ahrens, and others have now shown that the more unsaturated the fat ingested, the more effective the diet is in lowering blood lipids. But whether this effect is due to poor absorption, better oxidation, or a vitaminlike role of these unsaturated fats has not been established. Many observations in animals have shown that the type of fat deposited in the depots or the blood vessels is dependent on the type of fat ingested.

Another established phenomenon is the presence of large quantities of polyunsaturated fatty acids in structural lipids. Holman has demonstrated an unsaturated fatty acid deficiency state in rats. However, no such deficiency syndrome has ever been reported in humans. In fact human red cells have now been shown to have the capacity of synthesizing unsaturated fatty acids from acetic acid in vitro. This observation, of course, rules out the notion that the polyunsaturated fatty acids are in the absolute sense vitamins in the human, except perhaps in some relative way. However, since the body fat can be changed by these dietary regimes and since the diseases under discussion here are related to either local or generalized fatty depositions, the therapeutic rationale for attempting to alter these states is obvious, and from experimental data thus far obtained does hold promise.

Drugs which either prevent the absorption of cholesterol (sitosterols) or block the synthesis of cholesterol (delta-4-cholesterone) are also under investigation. However, the eye with its protean manifestations of these diseases, along with its unique susceptibility to undisturbed observations, should admirably serve as an excellent parameter for the therapeutic assay of these new agents.

Summary

Cases are presented having ocular lesions characterized by deposition of fats. These lesions are described and classified in relation to the lipid content of the blood. The significance of the ocular lesion as an aid in diagnosis of the underlying metabolic disorders is discussed. The possible effect of dietary control through restriction or regulation of fat intake in the prevention or retardation of the development of the ocular lesion is noted.

Duke Hospital.

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PERIPHERAL IRIDOTOMIES

For round-pupil cataract extractions

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In 1929, I saw Elschnig perform peripheral iridotomies for round-pupil cataract extractions. He did it so quickly and easily and with a minimum of trauma that it immediately appealed to me. However, comparatively few surgeons have adopted the procedure and there are remarkably few references to it in the literature. The purpose of this communication is to call attention to this excellent method of making an iridotomy.

In 1911 and 1912, papers by Elschnig[1] stated that, "Influenced by the results, which were made public at the Budapest International Congress of Medicine in 1909, I commenced using the peripheral incision advocated by Bajardi in 1895, and up to the 15th of February, 1912, have operated 287 eyes by this method."

Elschnig described the procedure, "After the regular incision and capsulotomy have been performed, the corneal flap is grasped with forceps and laid back. The iris, completely exposed, is then incised close to the scleral lip of the wound with the small pointed branch of a deWecker (Esbach scissors) practically raising a fold of the iris and making an incision about one-mm. long parallel to the edge of the cornea."

As the intracapsular cataract extraction with round pupil developed and became more popular, Elschnig continued to use this method of making a hole in the iris to prevent iris prolapse.

His method of performing the iridotomy in 1929 was: On completion of a full Graefe section with a conjunctival flap, the wound was opened by traction on the conjunctival flap with forceps to expose the iris. A fold of iris was produced by engaging it with the pointed blade of deWecker scissors close to the scleral lip, near the root of the iris. The fold was then cut by closing the scissors to produce the iridotomy.

The first objection to this method that occurred to me was that the capsule or zonule

might be injured by the point of the scissors. Elschnig assured me that this did not occur. On returning home I did iridotomies in a similar manner on pigs' and cats' eyes. In some of the eyes the corneas were removed at the limbus and iridotomies were done around the whole circumference of the iris close to the base. In each of these eyes the iris was then removed and the lens and zonule examined with a loupe. No injury to either was observed.

This method of making an iridotomy has been used in all of my round-pupil extractions since that time, a period of about 27 years. At first, only one iridotomy was made at the 12-o'clock position, following Elschnig's procedure. Later two, then three, iridotomies were made as the type and number of corneoscleral sutures were changed. Larger iridotomies were made when pupil block was emphasized by Chandler.[2]

Until 1957, I have used deWecker scissors with both blades pointed and the same length. In no instance in which the capsule ruptured during extraction have I felt that it was caused by the scissors but mostly to poor technique or an unusually friable capsule, such as those encountered in intumescent cataracts. My percentage of extractions in capsule has been about the same as that reported by others and it has increased as my technique improved. In a series of 300 cataract extractions published in 1945[3] 87.4 percent were extracted in capsule; in my last 500 extractions 95 percent were extracted in capsule, which would indicate that comparatively few if any capsules were injured by the deWecker scissors in making the iridotomies.

The risk of damage to the zonule or face of the vitreous leading to loss of vitreous is indeed remote, which is verified by the following series of cataract extractions. In my last 500 extractions vitreous was lost in three cases. In one case, it occurred during a loupe delivery of a dislocated lens in which no iridotomy was done. In the second instance it occurred in a linear extraction of a congenital cataract. In the third case, vitreous was lost by inadvertently exerting too much pressure on the eye after the lens was extracted.

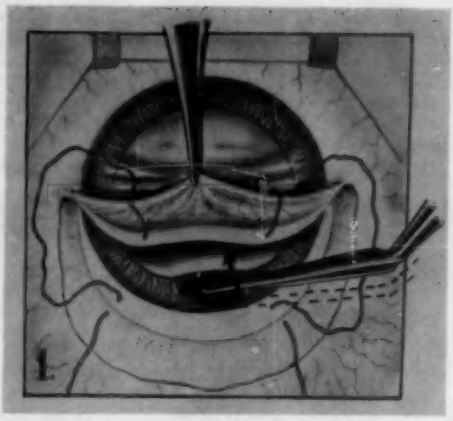

Fig. 1 (Atkinson). Corneal flap raised with forceps and iris stroked down with blades of scissors.

My associate, Dr. Kennedy, has watched the procedure done with sharp-pointed deWecker scissors for over six years. He states that in no instance has he observed a complication attributable to this method of making the iridotomies but the *apparent* risk of such an occurrence deterred him from adopting the procedure. This year deWecker scissors with blunt ends on both blades have been used and to my surprise it is as easy to produce a fold of the iris and perform the iridotomy with the blunt-pointed scissors as it was with sharp-pointed ones. When the change was made to the blunt-pointed scissors Dr. Kennedy adopted the procedure immediately.

With this change which seems safer, more surgeons may be influenced to use this excellent method of making an iridotomy for round-pupil cataract extractions.

The technique is as follows: The corneal flap is raised and the iris gently stroked down with the closed blades of the scissors (fig. 1) to expose the iris so that the iridotomy can be made in the periphery. The ends of the blades are then directed upward and backward toward the limbus (fig. 2). In this location there is ample space between the iris and the vitreous so that with moder-

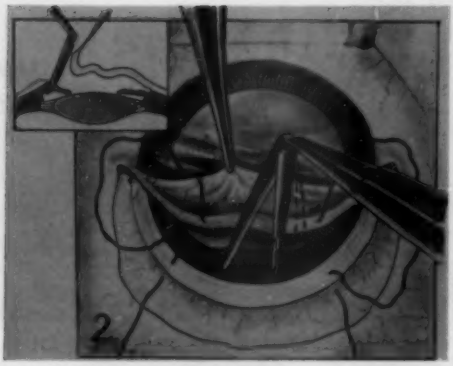

Fig. 2 (Atkinson). Blades of scissors directed upward and backward toward limbus and close to upper lip of wound. A fold of iris is caught up on the tip of one blade and cut. The insert shows the angle of the scissors to make the iridotomy in the periphery of the iris well away from the lens and zonule.

ate care it is not injured. The end of one blade is pressed gently against the iris close to the upper lip of the wound and moved in the direction of the other blade, parallel to the limbus. In this way a fold of the iris is produced between the blades. When the fold is of the desired size, the blades are closed cutting the fold. The postoperative appearance is shown in Figure 3.

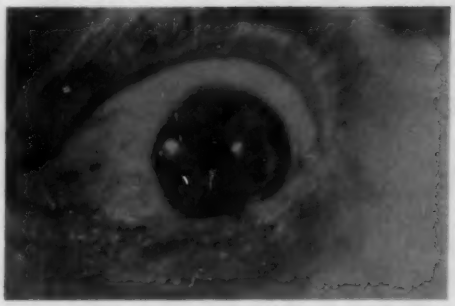

Fig. 3 (Atkinson). Postoperative appearance of the iridotomies.

Conclusion

Following this technique, a peripheral iridotomy can be made safely and easily, with a minimum of trauma and without the use of iris forceps or the aid of an assistant.

129 Clinton Street.

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ANGIONEUROTIC EDEMA OF THE ORBIT*

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"Angioneurotic edema (Quincke's disease) occurs in individuals who are allergic to certain foods and infections, and in a group where no causative factors can be determined other than that the individuals are usually of neurotic temperament."† This statement taken from a well-known textbook on clinical neuro-ophthalmology summarizes our present knowledge of a troublesome, recurrent, pathologic, allergic reaction involving local tissues without regard to anatomic situation or embryologic origin. The parts involved such as the lips, face, eyes, limbs, trunk, or the nervous system are not delimited by the area of distribution of any one of the branches of the nervous system—in fact, there appears no basis, anatomic or func-

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*Read at the Seventh Congress of the Pan-Pacific Surgical Association, November 14-22, 1957, Honolulu, Hawaii.

† Walsh, F. B.: Clinical Neuro-Ophthalmology. Baltimore, Williams & Wilkins, 1947.

Fig. 1 (Benedict). Between attacks for nearly 25 years the appearance of the right eye and face returned to normal.

tional, to account for the time, place, and extent of the attacks nor are they associated with any physiologic function. The most characteristic feature of the disease is its recurrence in frequent irregular episodes of nearly the same extent and duration followed by a return to normal of all tissues involved.

Important factors in all types of allergic response are an hereditary history, eosinophilia, favorable reaction to epinephrine and low blood pressure. In general, it is a disease found in children and young adults who are demonstrably allergic to foods, infections, light, and climate. The diagnosis is sometimes difficult because of the similarity of symptoms of other diseases. Most cases are mild but severe attacks of edema lead to optic neuritis, papilledema, glaucoma, hemianopsia, deafness, convulsions, and a variety of peripheral palsies. Patients often recover after withdrawal of food, milk, or removal of infection and intestinal parasites.

Occasionally swelling of the eyelids and exophthalmos are seen as a result of angio-

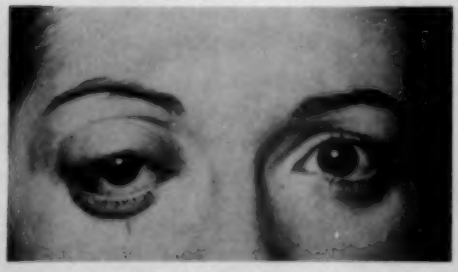

Fig. 2 (Benedict). Proptosis of right eye, edema of lids, and conjunctival injection at height of average attack.

Fig. 3 (Benedict). Persistent proptosis between attacks.

neurotic edema involving the orbit, with paralysis of the extraocular muscles and temporary loss of vision. Recovery is the rule when the exciting agent can be removed. Some cases become chronic, resulting in permanent paralysis of the eye muscles and alteration in the field of vision or partial blindness. While most cases are bilateral,

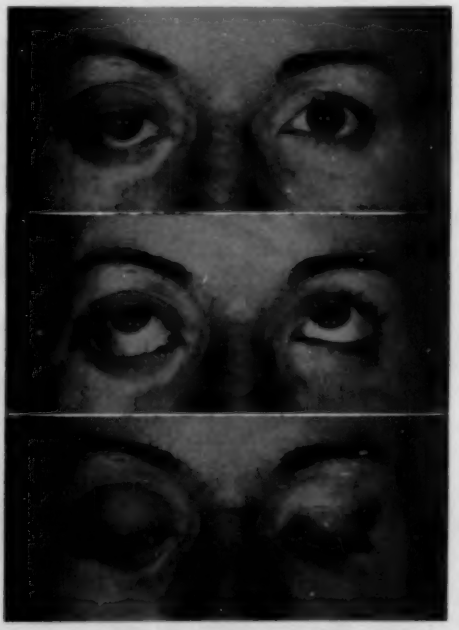

Fig. 4 (Benedict). Proptosis and limitation of movement of the right eye.

others are alternately unilateral; and some that begin as bilateral later have episodes on only one side. The search for infection and parasites may be negative, and the response to adrenalin, the occurrence of eosinophilia, and the history of heredity may be absent in a clinically typical case of angioneurotic edema with exophthalmos. Observation of such a case is worth recording because of the negative clinical tests, negative physical and laboratory findings and conflicting medical advice.

Case report

Miss M. K. R. had been a healthy child except for mild hay fever and she had had no serious illness until at the age of 13 years she suffered a sudden and unexplained edema of the left eyelids. It was painless and remained unchanged for two days then it quickly disappeared. Two months later a swelling appeared at the right nasolabial fold and was diagnosed as a cyst. A week later it spontaneously disappeared. Three months later she developed a severe edema of the lids of both eyes associated with a reddish-blue butterfly lesion of the face with raised, marked swelling which was very painful. The condition lasted 10 days and rapidly disappeared.

After a succession of attacks of painful edema of the face and eyelids, she recalled that her cousin had brought her a straw basket from South America and it was presumed that her attacks of edema might have been instigated by an allergic reaction to something about the basket. Blood tests for Chagas' disease were made but results were indecisive.

For the next 12 years she suffered recurrent attacks of edema of the face and eyelids lasting from three days to three weeks at intervals of two to eight weeks. Edema occurred over the cheek bones and in the eyelids, usually bilateral. The attacks were usually severe with the eyelids bluish in appearance and swollen shut.

During the attacks the visual acuity was not diminished and there was no involvement of the cornea, conjunctiva, or the orbit. Following the subsidence of the edema, the lids and face were normal in appearance and there was no noticeable sequelae. Her general health remained good. There could be found no relationship between the episodes of facial edema and any physiologic function, climate, food, infection, occupation, or clothing.

At the age of 25 years, during a usual attack, a series of X-ray treatments were given to the face and eyelids, as shown in Table 1.

Following the first X-ray treatments of this series, the edema disappeared as usual but from that time the character of the attacks was markedly different.

TABLE 1

Record of X-ray treatments

Date	Kv.	Filter (mm. al)	Distance (inches)	r	Location
3-30-44	100	2	10	100	Glabella
4- 6-44	100	2	10	100	Right temple
4-11-44	100	2	10	100	Left temple
4-13-44	100	2	10	100	Glabella
4-18-44	100	2	10	100	Right temple
4-24-44	100	2	10	100	Left temple
4-27-44	100	2	10	100	Right temple
5- 2-44	100	2	10	100	Glabella
5- 4-44	100	2	10	100	Left temple
10-21-44	100	2	10	100	Glabella
10-28-44	100	2	10	100	Glabella
11- 2-44	100	2	10	100	Glabella
10-20-45	100	2	10	100	Right temple
5-16-46	100	2	10	100	Right temple
12- 3-46	100	2	10	100	Right temple
7- 1-47	100	2	10	100	Right temple
7-15-47	100	2	10	100	Right temple

Subsequent attacks have occurred at intervals of four to seven weeks, limited to the right side of the head. They are initiated by two days of a feeling of exhaustion, then a severe right hemicrania for one or two days. The headache may be partially relieved by aspirin but invariably the right forehead, eyelids, and orbit became markedly edematous, the eye proptosed, and the vision blurred. The headache gradually diminishes but the edema and proptosis persists for five to 15 days. Similar episodes have appeared at intervals of 10 days to three weeks.

More recently, during the past five years, the proptosis of the right eye has not completely subsided between attacks and she now has persistent exophthalmos of the right eye, with diplopia. At the height of the attack there is an exophthalmos of five to eight diopters, the fundus shows papilledema of two to four diopters, and visual acuity is reduced from 6/6, to light perception. Between attacks the vision returns to 6/6, the papilledema disappears, and she has no pain. Edema of the eyelids and forehead disappears entirely after each attack. At no time during the attacks of orbital edema, has chemosis been noted. The cornea has not been clouded.

Physical and neurologic examinations have revealed no clues to the cause of the edema. The attacks usually are more severe in warm climates and in hot weather but are not aggravated by colds. She has not had a severe attack of edema during a head cold. She has no associated symptoms such as sweating, flushing, and throbbing. Some tightening of the skin over the forehead led one consultant to a suggestive diagnosis of scleroderma.

Roentgenograms show very slight increase in density of the right orbit as compared with the left, and a cyst in the floor of the right antrum. The skull is otherwise negative.

Physical examination and laboratory tests done

between attacks give vision: R.E., 6/6, 14/14; L.E., 6/6, 14/14. Pupils are normal, reflexes normal, fields normal, fundus negative. Exophthalmometer: R.E., 24,; L.E., 17 at 92. Diplopia beyond 15 degrees rotation in all directions. Culture-swabs from nasopharynx: Corynebacterium one, species seven. Basal metabolism, plus four, weight 120 lb., SBP 98, DBP 71, Kline negative, cholesterol 177, serum protein 6.57, albumin 4.04, globulin 2.53. Hemoglobin 12.7, lymphocytes 32.5, monocytes five, neutrophils 61, eosinophils 1.5. No symptoms of endocrine disorder.

Neurologic consultants reported the central nervous system as negative. The history, according to one consultant, "is very suggestive of longitudinal sinus thrombosis, with characteristic proptosis, conjunctival injection, swellings about the forehead, and retinal venous distention. However, she had a localized pitting edema above the right eyebrow which was very definite. In the past these swellings occurred in the lower face and could hardly be related to a venous congestion. Crowe's sign was not positive." There was no dilatation of the retinal veins during contralateral jugular obstruction. There was no proof of intracranial venous obstruction. An electroencephalogram showed "dysrythmia grade 1."

Neurologic examination showed no evidence of a space-taking intracranial lesion, although X-ray films of the skull showed the right orbit to be smaller than the left and a slight thickening of the bone. Between episodes of edema there is no abnormal palpable mass in the right orbit. Now that proptosis is persistent, the orbital tissues seem thick to the fingers and the proptosed globe cannot be pushed backward.

During two months of observation and treatment at the Mayo Clinic (1949), she had an extensive trial of histamine therapy and a brief trial of antihistaminics, all without avail in forestalling or preventing recurrent attacks. Following two X-ray treatments to the right orbit (in May, 1949) there were no attacks for seven weeks, the longest remission in the past four years and no severe attacks for at least three months. Former X-ray treatments were also of no therapeutic value.

In April, 1956, she was thoroughly examined in a large Eastern clinic. Apart from the right exophthalmos and motility restrictions of the right eye, the examination was entirely negative. Again in April, 1957, she returned to the Mayo Clinic where extensive physical examination was repeated and a number of sensitivity tests were given. A marked skin reaction (Schwartzman type) followed injection of a filtrate from a culture obtained from a pharyngeal swab. Subsequent injections caused such severe skin reactions that they were discontinued. They had no effect on the edema and did not defer an attack. The cyst in the right antrum, disclosed by X rays, was considered of no significance.

During the past five years the episodes of edema have continued at irregular intervals with gradually increasing severity. Preceded by two days of a feeling of exhaustion, the pain in the right side of the head and face and the neck reaches such severity that she has been compelled to leave her job as a bookkeeper and she has been out of employment for months at a time. Between attacks she is free from pain; there is no edema of the orbit, eyelids, or face; however, proptosis of the right eye of two to four mm., with restricted movements, persists.

Comment

In a survey of the literature on the subject of angioneurotic edema, I have not found a case report of orbital and intracranial involvement of such duration, nor with a similar clinical course. While in many respects it seems to be an uncomplicated case of Quincke's disease, some consultants have denied it, other concurred, and still others, mostly ophthalmic surgeons, have diagnosed a space-taking lesion within the right orbit and have urged surgical exploration.

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IS FLUORESCENT LIGHTING INJURIOUS TO THE EYES?*

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New York

Experimental use of fluorescent materials for lighting dates back a century ago. Practical application in sign tubing started in the early 1930's. A commercially available tube with internal phosphor coating for general lighting became available in the mid-1920s. Without such phosphor coating, the fluorescent tube was essentially a low-pressure mercury-vapor lamp. This development was the outcome of research, begun almost 10 years earlier, on the optimum mercury-vapor pressure for the production of ultraviolet radiation and desirable phospho characteristics.[1]

After 1938, when fluorscent lamps became available commercially, fluorescent lighting was regarded by certain investigators as possessing harmful qualities not found in other forms of artificial illumination or in daylight.[2-6] One reason for this concept was that in early fluorescent installations the bare tubes were too bright. This defect, however, was eliminated by the design of well-shielded luminaires. Other attributes peculiar to this specific type of light source, which were frequently cited as causing adverse ocular effects, were flicker, stroboscopic effect, color characteristics of the tubes, and ultraviolet radiation.

This paper summarizes the literature on ocular effects of fluorescent lighting in historical perspective. Three types of radiation involved in fluorescent light sources have been investigated, namely short-wave or far, medium wavelength or erythemal, and longer wavelength—ultraviolet or near. The conclusion, based on this review, is that when fluorescent lighting is properly installed and maintained, no harmful effects are produced on normal human eyes in healthy individuals. Other investigators have confirmed this conclusion.[7,8] However, previous work of the authors[9,10] and other studies[7,11] have indicated a need for further evaluation of present-day fluorescent illumination. This is included in the following discussion.

FLICKER AND STROBOSCOPIC EFFECT

The most common objection to fluorescent lighting has appeared to be the stroboscopic effect or flicker.[12] Any bulb or tube operated on an alternating-current circuit has a fluctuating light output caused by pulsating variations in current, called "cycles," and described in terms of frequency of 25, 50, or 60 cycles. This is most noticeable in low-wattage incandescent filament bulbs operated at frequencies below 50 cycles. In incandescent bulbs the light is interrupted each time the electricity changes direction, that is 120 times per second for 60-cycle frequency. For years western New York State and the Province of Ontario, Canada, operated on 25-cycle frequency. While the residents became completely accustomed to it, visitors from 60-cycle regions complained of distractions and some of discomfort.

The long-persistence phosphors now being used as coating in fluorescent tubes have minimized flicker on 60-cycle circuits. With these tubes the light output fluctuates between a maximum and minimum but never goes out completely when the electricity changes direction. Where two or more lamps are mounted close together, they can be operated on different pulses (out-of-phase, using two lamp ballasts or utilizing all phases of a three-phase power supply). Thus, one tube is giving its maximum light output when

* Aided by a grant from The Ophthalmological Foundation, Inc., and from the Research Department of the New York Association for the Blind, and from the Department of Ophthalmology, New York University Post-Graduate Medical School. Technical development through Office of the Technical Director, Illuminating Engineering Society.

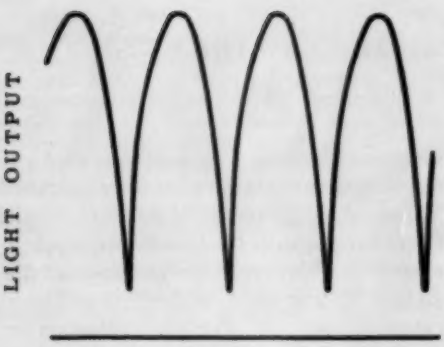

Fig. 1 (Berens and Crouch). Light output from three fluorescent tubes all operated on a single phase (same pulse of current). (J. Segal.[14])

a neighboring one is at its minimum. In 1944, the National Bureau of Standards[13] reported that "flickering of fluorescent lights should cause no noticeable fatiguing of the eye nor should it cause any permanent injury to the eye."

Segal,[14] however, stated that reading for four hours under three shielded daylight fluroescent tubes operating in phase on 50-cycle frequency (fig. 1) resulted in measurable visual fatigue. His criterion for the diagnosis of visual fatigue was the time required to adapt thé eyes sufficiently to recognize the position of a Landolt ring projected on a screen with a contrast of only four percent. Reading under tubes operated on the three phases of a three-phase supply (fig. 2) produced no evidence of fatigue. Illumination from two tubes fed on two phases of a three-phase supply produced just measurable fatigue. With reference to these results, however, the phosphors used in daylight tubes had less "hold-over" than current white tubes. In addition, the tubes tested may not have had the long-persistence phosphors now in use here and abroad.

Gray and Prevetta[15] compared the effects of two hours of continuous reading under daylight as compared with two hours of continuous reading under fluorescent lights. They found that fluorescent light of 20 foot-candles intensity was not inferior to daylight of the same intensity for reading eight point type material.

Flickering or flashing light sources give the effect of a rapid series of pictures. If such a tube is used to illuminate a moving object and is timed so that it always emits light when the object is in the same position, the object appears to stand still. This stroboscopic effect may occur with all tubes operated on a given pulse of alternating (pulsating) current. It is also marked in any lamp functioning on the gas discharge principle.[12] The stroboscopic effect is evidenced by apparent slowing down, stopping, or even reverse motion of rotating or oscillating objects. These fluctuations often appear to give fast moving machinery a jerkiness.[12] Such illusions proved dangerous in the early days of fluorescent lighting when workmen attempted to touch machines which appeared to be stationary. However, the stroboscopic effect is greatly reduced by the characteristics of the newer tubes and by the use of differing current pulses (different phases).

Series ballasts were developed about 1950. By means of these ballasts tubes operate in phase (the same pulse). Some stroboscopic effect is still produced but no noticeable flicker. With present fluorescent phosphors, objects rotating at speeds which are exact multiples of the frequency of the electric supply, when viewed under tubes operating

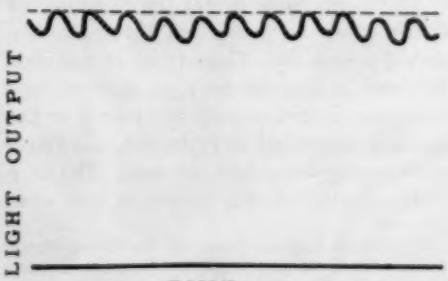

Fig. 2 (Berens and Crouch). Light output from three fluorescent tubes each operated on a different phase of a three-phase electrical supply. (J. Segal.[14])

on series ballasts, have two images, one rotating and the other standing still.[16] However, since there is not just a single image standing still, it is doubtful that a machine operator could fail to realize that the equipment was moving. Therefore, stroboscopic effects are no longer considered by us as a serious source of complaints concerning fluorescent lighting.

Color contrasts of fluorescent tubes and incandescent filament bulbs

Baumgardt[17] has shown that visual acuity is slightly less under a given level of illumination provided by daylight (blue) fluorescent tubes than under an equal amount of light from incandescent filament bulbs. This is in agreement with the fact, previously established by Pieron,[18] that visual acuity is poorer in blue light than in white, red, yellow, or green light. He explained this phenomenon by the fact that the emmetropic eye is myopic in blue light. Baumgardt[17] presented the results for 13 observers to show that, on the average, 1.22 as much daylight (blue) fluorescent (1949) light is required as incandescent (yellow) light to produce the same visual acuity. Studies by Simonson and Brozek[19] indicated slightly less visual fatigue after a two-hour period of visual work under greenish incandescent lighting than under white incandescent lighting with a slightly bluish cast or ordinary inside frosted filament lamps. These authors measured visual fatigue by the drop in performance in recognizing small letters appearing irregularly in a vertical slot.

Aside from these effects the spectral quality of the visible light has little if any effect on vision. According to White, Solandt, and Rosen[20] the spectral composition of white light does not affect visual acuity. They found no significant differences in the visual effectiveness of white light from four sources, namely, (1) a zirconium concentrated arc lamp with fairly even emission over the entire visible spectrum, (2) a 25-watt circular white fluorescent tube, and (3) and (4) two sources of white light produced by mixing two and three narrow spectral bands of complementary colors.

In a study by Hassel[21] it was found that visual performance (measured by the Landolt ring test) was slightly greater under low (one to two foot-candles) levels of incandescent lighting than under the same level of daylight-color fluorescent light. This effect was reversed as the illumination was increased to five foot-candles. Both sources were operated on direct current to avoid flicker effects. At 10 to 20 foot-candles color seemed to produce no difference in central vision, but in regard to peripheral vision fluorescent lighting was relatively slightly better than incandescent at 50 foot-candles than at 10. However, the effect of illumination level on performance with peripheral vision is not nearly so great as with central vision.

Visual asthenopia has been considered a subjective result of a disproportion between the quantity of illumination and the color of the light—impression of coldness. Asthenopia with conjunctival irritation may be observed. However, these findings in addition to dazzling, diminution of contrasts and shade, and stroboscopic effect were attributed by Michal[22] to inexpert installation of fluorescent lighting with inadequate quantity.

Short-wave ultraviolet radiation (below *290* μ)

The fear of the effects of ultraviolet radiation emitted by fluorescent tubes is thought to be groundless as there is none of shorter wavelength than that found in diffuse daylight.[12] Moreover, the very short-wave length ultraviolet radiation within fluorescent tubes which might cause vesiculation of the skin is completely filtered out by the tube glass. Studies by the United States National Bureau of Standards[23] indicate that in comparison with a mercury arc used as a standard of germicidal ultraviolet radiation and with a sensitivity of one part in 50,000 it was impossible to detect any 253.7 millimicron ra-

diation at a distance of four inches from fluorescent lamps. Ruff,[24] using an instrument capable of measuring accurately one hundred-thousandth of a watt per square foot, was able to detect no 253.7 millimicron radiation, even immediately adjacent to the tube wall of a standard fluorescent tube.

At the 1948 Paris meeting of the International Commission on Illumination it was generally accepted that an intensity of one-ten-thousandth of a watt per square foot of 253.7 millimicron ultraviolet is safe, even for small children exposed for periods of 24 hours per day. Duke-Elder[25] has stated that for practical purposes only short-wave ultraviolet radiation below 300 μ may be considered to have any abiotic effect on the eye, and then only at an intensity of at least 2,000,000 erg-seconds per square cm. (186 watt-seconds per square foot or 0.00214 watts per square foot per 24 hours). Similar data were published by Verhoeff and Bell,[26] who found exposure to one-sixth the liminal radiation (186/6 or about 31 watt-seconds per square foot) repeated every 24 hours for 52 days had no visible effect on the cornea or on the conjunctiva. An exposure of one-third the liminal (about 60 watt-seconds per square foot of short-wave ultraviolet) repeated every 48 hours had only a slight effect on the cornea after seven to nine exposures, and then disappeared even with additional exposures.

Medium ultraviolet radiation

Medium ultraviolet radiation (290 to 325 millimicrons) can have erythemal (sunburning) effects and may cause corneal irritation.

Most research workers[24, 27, 28] agree that illumination of the order of 50 foot-candles from fluorescent tubes contains less than one one-hundredth as much sunburning radiation as summer noon sunshine. Latarjet[27] stated that no illumination level less than about 200 foot-candles (from fluorescent tubes) can produce reddening of the skin. He mentioned that higher levels are required to produce an effect on the cornea. However, he reported that about 20 percent of the population have a threshold for erythemal effect much lower than the mean and that subjects having hyperthyroid, diabetic, sympathicotonic, or hepatic conditions are subject to low threshold. Less than one in 1,000 have a threshold about one-tenth that of the mean.

Rutgers[29] found that for a 40-watt Philips TL fluorescent tube the ultraviolet radiation shorter than 315 millimicrons on a plane one meter from the tube amounts to 2.7 erg/cm.^{2} sec. (0.00025 watts/sq. ft.). He concluded that for normal persons it takes at least 24 hours to produce either erythema of the skin or conjunctivitis under an illumination level of 100 foot-candles.

In LeGrand's[30] research one group of rabbits was subjected to fluorescent lighting and another to an equivalent amount of incandescent light. No changes were noted in the lens after close exposure (18 foot-candles at 50 cm. from the animals' eyes) for a period of nine months. During this period, the animals were killed and examined periodically. A slight decrease in clarity of the crystalline lens was observed after about six months' time but with no significant difference between the two lighting systems.

In a similar study Kline and Rusch[31] placed two groups of albino mice directly under the light of two daylight fluorescent tubes for periods of four to six hours a day, six days a week, for one year. The ears of one group were painted with mineral oil to facilitate the penetration of the rays into the skin. Although the total amount of radiant energy applied over the total period was considerable, the intensity of ultraviolet radiations in the 312.5 millimicron band was very low. There was no evidence of erythema, or neoplastic changes of the skin, or of irritation of the cornea.

Long-wave ultraviolet radiation

At the suggestion of one of us (C. B.) and through a request of the Illuminating Engineering Society, the United States Na-

tional Bureau of Standards in 1954 measured the long-wave ultraviolet output of five 40-watt standard cool white fluorescent tubes from three manufacturers and one 500-watt inside-frosted incandescent filament bulb. The total radiation measured every five millimicrons from 300 to 400 millimicrons at a point three meters distant from the lamps averaged as follows:

500-watt incandescent	0.631 μw/cm²
40-watt cool white fluorescent	0.303 μw/cm²
Summer noon sunshine at Sacramento Peak, New Mexico	7203. μw/cm²

Assuming 2,400 lumens initial seasoned output from the fluorescent tubes, 9,900 lumens from the incandescent, and an illumination of 8,500 foot-candles from the sun, these sources give the following outputs of 300 to 400 millimicron ultraviolet per lumen:

500-watt incandescent	60 μw/lumen
40-watt cool white fluorescent	88 μw/lumen
Summer noon sunshine at Sacramento Peak, New Mexico	780 μw/lumen

The actual amounts of energy present outdoors and in typical interiors can be obtained by multiplying these values by the levels of illumination normally obtained with each source. Assuming 4,000 to 8,500 foot-candles outdoors from daylight and 50 foot-candles indoors, the radiation from noon sunlight is 500 to 1,200 times as much as a good office or school lighting installation; the difference between fluorescent and incandescent filament lamps is one-and-one-half as much.

Verhoeff and Bell[26] stated that no injurious effects of radiation in the 300 to 400 μ range had ever been found with any degree of certainty. Since this range of radiation is present in considerable amount in sunlight they concluded that any harmful effects would have been eliminated by the process of evolution.

Allphin[11] reported on a field test planned for the purpose of determining whether the few individuals who are particularly sensitive to light, and who may really need to wear tinted lenses outdoors in sunlight, might be affected by the slight amount of long-wave ultraviolet radiation in fluorescent lighting. Two groups of workers were placed in similar offices in a new building, but, without their knowledge, half of them worked under standard white fluorescent tubes and half under white tubes coated with a plastic solution, which cut off radiation below 400 μ with no appreciable effect on visible radiation. No indicative difference in reaction to the lighting systems was found. The 81 individuals included in this study worked for three months with no criticism being made of the lighting before they were interrogated. On the basis of this, Allphin concluded that the small amount of ultraviolet radiation present in standard fluorescent tubes causes no specific visual difficulty.

In the same article Allphin mentioned an individual who considered himself unusually sensitive to fluorescent lighting, and, therefore, wore tinted lenses over his regular eye glasses. Four pairs of tinted slip-on lenses were prepared, two of which absorbed ultraviolet and two of which transmitted it. The subject, without knowledge of the character of the lenses, was asked to wear his own glasses and the four new pairs, in any order he chose, for one week each. At the end of the five-week period he felt that all of the glasses relieved his discomfort equally well and concluded that he was equally as sensitive to sunlight and incandescent lighting as to fluorescent illumination.

Even though there is a slight amount of long-wave ultraviolet radiation in fluorescent illumination, school children and industrial and office workers seldom view a lamp directly. Much of the energy which the eye receives is reflected from various surfaces in the room, and most such surfaces reflect considerably lower percentages of ultarviolet energy than visible light (table 1).[32] Therefore, the net amount of ultraviolet energy at the eye is far below any maximal tolerable limit.

The effect of long-wave radiation on the

TABLE 1

REFLECTANCES (LUCKIESH[38])

	Percent	
	365 mμ Ultraviolet	Visible Light
White wall plaster	76	90
Kalsomine white water paint	40	70
White porcelain enamel	63	80
Wall paper samples:		
Ivory	49	64
White	45	69
Pink figures	49	64
Ivory figures	50	75
Brownish figures	33	55

dark adaptation of the eye is a controversial subject. Experiments by Sexton, Malone, and Farnsworth[33] with observers reading under illumination from white fluorescent, ultraviolet-shielded white fluorescent, and daylight incandescent lamps of 20 foot-lamberts brightness showed no difference in dark adaptation or visual acuity curves (using Landolt ring tests) through a four-hour period, after an initial one hour preadaptation period. These investigators did find a difference in dark adaptation after exposure to a brightness of 165 foot-lamberts from a quartz-mercury lamp (ultraviolet transmitting) but no experiments were made using fluorescent lamps at this brightness level.

Wolf has published several papers[34–39] in which he stated that the long-ultraviolet (315 to 380 millimicrons) present in sunlight, and to a lesser extent in light from fluorescent tubes, reduces night visibility even though no pathologic changes can be observed in the eyes. Wolf interpreted this loss in dark adaptation as indicative of a decrease in overall visual sensitivity. He showed this decrease for eyes exposed to unshielded mercury-vapor tubes and fluorescent tubes and also reported that the effect disappears when the mercury tubes are shielded by their usual glass jackets or when filters with a cutoff of about 400 millimicrons are used with fluorescent tubes. Experiments with aphakic observers showed a greater decrease in dark adaptation since normally the crystalline lens absorbs much of the ultraviolet which would otherwise reach the retina.

Wald,[40] in a discussion of the alleged effects of the ultraviolet on human vision, reported that he was unable to obtain data similar to Wolf's using the same experimental setup and one of the same subjects. According to Wald, the cornea absorbs almost all incident radiation below 300 millimicrons and the crystalline lens (yellowish) has a very sharp cutoff at 400 millimicrons. Therefore, it seems unlikely that crown or Pyrex glass filters, which have a more gradual cutoff between 300 and 400 millimicrons, and Noviol A, which cuts off slightly above 400 millimicrons, should have any difference in effect of the nature shown by Wolf. Wald also questioned why Wolf's difference in loss of adaptation between normal and aphakic eyes should not be far greater, since without the lens a much greater magnitude (on the order of 1,000 times more) of long-wave ultraviolet energy reaches the retina. In Wald's experiments with aphakic subjects the cones were affected rather than the rods, the difference in performance resulting from the change in brightness because of greater transmission of the eye media with the lens removed.

Dark adaptation and the near ultraviolet were also investigated by Moeller and his associates,[41] who found no reliable evidence that exposure to near ultraviolet affects dark adaptation deleteriously. They were unable to identify the source of the discrepancy between the negative and positive findings reported by other investigators. These authorities suggest that the positive findings may result from the influence of a very complex set of factors. An example of this hypothesis is the work of Wolf and Zigler,[42] in which exposure of the right eye to a light adaptation field, which had ultraviolet components, raised the final dark adaptation for the left eye.

SUMMARY

Many of the early objections to fluorescent lighting have been overcome by improve-

ments in the design of the tubes and by careful installation, so that dazzling, flickering, and stroboscopic effects have been largely eliminated.

Investigations have shown that visual acuity is poorer in a daylight (blue) fluorescent illumination than under the same amount of light from incandescent filament bulbs. Another finding is that visual acuity is not affected by the spectral composition of white light.

The short-wave ultraviolet radiation emitted by fluorescent lamps is not considered detrimental to the normal eye. Even the medium ultraviolet radiation is judged to be harmless. A study of long-wave ultraviolet radiation by the United States National Bureau of Standards, made at our request, revealed that the radiation from noon sunlight is 500 to 1,200 times as much as a good office or school lighting installation, while the difference between fluorescent and incandescent filament lamps is only one-and-one-half as much. These data are based on the assumption that 4,000 to 8,500 foot-candles are obtained outdoors from daylight and 50 foot-candles indoors.

Although fluorescent illumination emits a slight amount of long-wave ultraviolet radiation, a lamp is seldom viewed directly. In addition, various surfaces of a room reflect most of the energy which the eye receives and they also reflect lower percentages of ultraviolet energy than visible light.

The effect of long-wave ultraviolet radiation on dark adaptation is a controversial subject, but evidence points to the probability that such radiation is not detrimental to dark adaptation.

Conclusion

From the preceding data and from personal observations in industry, offices, and a large school installation,[9] we conclude that when fluorescent tubes are installed and maintained with proper shielding so that they are not glaring, they have no harmful effects on the eyes or skin of healthy individuals.

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COMITANT CONVERGENT STRABISMUS WITH ACUTE ONSET*

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Comitant convergent strabismus arises not only in infancy and early childhood. It may make its first appearance in older children, in adults, and even in old people. It occurs then more or less acutely, accompanied by diplopia. Strabismus of late onset has interesting theoretical and practical implications. We shall discuss in this paper the various forms of acute comitant esotropia which have been described.

I. ACUTE ONSET OF COMITANT CONVERGENT STRABISMUS FOLLOWING ARTIFICIAL INTERRUPTION OF FUSION

The best known type of acute strabismus is the one in which a deviation occurs following patching of one eye or loss of vision in one eye from disease or injury. In adults it usually takes the form of exotropia. In children and young adults esotropia predominates. Many ophthalmologists have had, for example, the experience that a child, whose eyes were originally straight, developed a manifest deviation with diplopia during therapeutic patching for amblyopia ex anopsia. Swan[1] has reported on two such cases; in a third, a 27-year-old man, there was no amblyopia. The occlusion had been prescribed for diagnostic purposes by a nonmedical refractionist.

In the presence of an amblyopia such an occurrence is not entirely unexpected, but it may also take place in cases in which it was not foreseen, as in the cases reported by Paufique[2] and Swan.[1] Paufique's patient was a young girl whose one eye had been bandaged for 10 days for a corneal foreign body. It is noteworthy that this girl had not only a vision of 1.0 in each eye, but was also emmetropic. It is easier to understand the occurrence of an esotropia if the patient who underwent the patching had an uncorrected hypermetropia, as did one of the patients cited by Swan, a nine-year-old boy. Both Paufique's and Swan's patients required surgery to obtain a full functional recovery.

Surgery was not required in a patient seen and treated by one of us (H. M. B.) and reported on by Bielschowsky.[3] This was a truly remarkable observation in that a large manifest deviation with diplopia established itself following bandaging of one eye for two days in a 14-year-old boy with undected and uncorrected hypermetropia of +5.0D., O.U. The deviation disappeared within a few days of intermittent wearing of a correction incorporating prisms. It remained latent over some years of observation even though the patient refused to wear his glasses once he had regained binocular vision. It was of interest in more than one respect that the patient's older brother had had surgery for esotropia two years prior to the incident referred to.

Occlusion of one eye represents a peripheral obstacle to binocular vision. The seat of the disturbance may also be of central nervous orgin. Thus one of us[4] observed a 17-year-old girl who, immediately following a slight concussion of the brain, developed a manifest exotropia with spontaneous diplopia but without any signs of paralysis of the extraocular muscles. This exotropia reduced itself to an exophoria as the patient's general condition improved.

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Discussion

Particularly the last two examples show very plainly the influence which a well-developed sensory machinery has on the motor system of the eyes. Sensorimotor fusion and binocular vision result when there is a balance between those forces which tend to keep the eyes properly aligned and those which tend to disrupt the alignment of the eyes. The forces keeping the eyes properly aligned are very strong in some individuals, so much so that they can overcome remarkably great obstacles. Even in the presence of an amblyopia ex anopsia the peripheral fusional mechanism can prevent a manifest deviation.

People who have such a strong sensory fusion mechanism have good binocular cooperation under all ordinary conditions of seeing, but will develop a manifest deviation under extremely abnormal conditions, for example, if there occurs an artificial interruption of binocular vision of some duration. In other people the forces keeping the eyes aligned are barely able to overcome those forces which tend to drive the eyes apart. Such individuals will develop a manifest deviation at the slightest provocation, even if only for a short period of time. The extent to which the "fusion faculty," so much maligned by some in the past 20 years, is or is not capable of overcoming the misalignment of the eyes, is surely an important factor in the etiology of manifest strabismus.

One cannot, however, assume that the etiology is the same in all cases in which a manifest deviation results from temporary or permanent suspension of fusion. While in many cases this suspension causes a preexisting condition, a latent deviation, to manifest itself, in others this is certainly not the case. The number of adults who develop a gross exotropia following partial or total loss of vision in one eye is too great to permit one to conclude that they all had a potential exotropia of sizable degree.

There are a number of persons in whom the obstacles to binocular vision happen to be so insignificant that even prolonged occlusion of one eye does not elicit a manifest deviation. These are the ones who are said to have orthophoria. If such a person loses the vision in one eye to a great extent, he may nevertheless develop an exotropia, increasing as time goes on. Here the exotropia must be caused not by pre-existing factors but by new factors which have become operative.

We do not know what these new factors are. It is unlikely that "diplopia-phobia" is the responsible mechanism in all the cases, since in many of them the remaining visual acuity in the diseased or injured eye is too low for a disturbing diplopia to be present. One could theorize that one factor might be a divergence impulse not held in check by other optomotor impulses. This, together with the lateroversion impulse which would then be required to keep the normal eye fixating, and which would be additive to the divergence impulse in the eye with poor acuity, would drive that eye even farther outward. Over the months or years an actual contracture of the lateral rectus muscle of the deviated eye may add itself and help to keep the eye in an exotropic position. It is to be hoped that electromyography may be of assistance in deciding whether or not such a sequence of events actually does occur.

II. Comitant convergent strabismus of the "Franceschetti type"

The considerations regarding the genesis of the strabismus following the artificial interruption of fusion may also be applicable to the form of acute convergent strabismus which has been designated by Moutinho[8] as the "Franceschetti type."

The strabismus in these patients is characterized by an acute onset with diplopia, a relatively large angle of squint, an absence of signs of paralysis, and good potential binocular co-operation. Occasionally the diplopia and the strabismus are at first intermittent for a longer or shorter period of time before they become constant. The refractive error is as a rule in the low hypermetropic range

and the accommodative element is minimal. In most of the patients no immediate cause for the onset of the strabismus can be ascertained, although in some of them a debilitating illness or a physical or psychic shock may precede the onset.

A few cases of esotropia with acute onset have been recorded in former years, but it is not always clear from the reports whether they belong in this category or not. For example, in Bailliart's case[6] he was able to correct the strabismus by a novocaine injection into the right medial rectus muscle of an eight-year-old girl who had suddenly acquired an intermittent esotropia after an emotional upset. The effectiveness of the novocaine injection would speak for a paretic rather than a comitant esotropia.

In 1945 Burian[7] published four cases of esotropia with acute onset with diplopia. The patients were from 11 to 72 years. In three of them the onset was intermittent. No signs of paralysis of an extraocular muscle were present in any of the patients; they all had low hypermetropic refractive errors and a visual acuity of 20/20 or better in each eye. The angle of squint ranged from 20 to 60 degrees. All patients showed good binocular co-operation and surgery resulted in an excellent functional result.

The importance of this type of esotropia has been particularly stressed by Franceschetti and his collaborators[8–10] who have reported on a number of patients, all of whom had the characteristics described. The case contributed by Meunier[11] was rather interesting in that it concerned an emmetropic girl, four years of age, who had a vision of 10/10 in each eye. In contrast to this, Moutinho's patient,[8] a 16-year-old girl, had a strabismus which was definitely accommodative in nature. Accordingly, the deviation was relieved by nonsurgical means. Schlossman[12] also observed three patients who acquired an acute strabismus with diplopia. Their ages ranged from 50 to 57 years, but only one of them had an esotropia, the other two were exotropic.

In 1956, two further publications appeared on the subject of acute esotropia. In one of them Shukla[13] described briefly the case of an 18-year-old girl with acute esotropia and diplopia which responded well to orthoptic treatment. The other publication, by Norbis and Malbrán,[14] was especially interesting, since these authors observed four siblings in all of whom an esotropia of rather large degree arose with diplopia at a relatively late age (from six to nine years). All were operated upon, but the functional result was not very good, although all had normal retinal correspondence. Only one of the four developed small fusional amplitudes. It is possible that the poor functional result was due to the fact that three of the four children came to treatment at a late date: two six years after the onset and one four years after the onset. Also, there was a considerable residual deviation after surgery in three of them.

We shall now report on some cases of acute convergent strabismus which we have seen more recently.

Case reports

Case 1

A white boy was first seen on July 31, 1951, when he was six and one-half years of age. There was no family history of strabismus. Turning in of the right eye of the boy occurred rather suddenly in December, 1950, shortly after he had entered school. At the same time the child complained of diplopia which gradually disappeared. For a time prior to the turning in of the right eye, the child had had some pains in his legs but had had no fever or any other manifestations of illness.

At the first visit it was found that the patient had an uncorrected visual acuity of: O.D., 6/21—1; O.S., 6/12—2 and that there was, without glasses, an esotropia of 35 arc degrees for distance and near, with preference for fixation with the left eye. The retinal correspondence was normal in all tests. There were no signs of paralysis of an extraocular muscle. Cycloplegic refraction revealed: O.D., +2.0D. sph. $\supset$ +2.0D. cyl. ax. 90°; O.D., +2.25D. sph. $\supset$ +1.0D. cyl. ax. 85°. These glasses were prescribed and occlusion of the left eye was ordered.

With this correction the angle of squint was reduced; fusional amplitudes were noted on the major amblyoscope and a slight amblyopia of the right eye (6/12) was corrected by occlusion. On December 6, 1951, the angle of squint with correction was

20$^{\Delta}$ of esotropia with 6$^{\Delta}$ RHT for distance and 30$^{\Delta}$ of esotropia with 3$^{\Delta}$ RHT for near. On March 12, 1952, a five-mm. recession of the right medial rectus muscle was performed which reduced the angle of squint for distance to 8$^{\Delta}$ and to 10$^{\Delta}$ for near with correction. In the ensuing years the boy continued to develop good amplitudes, but some exotropia appeared. The spherical correction was reduced in power and energetic orthoptic treatment was instituted.

On February 24, 1956, he was again wearing a full correction for his refractive error (O.D., +2.0D. sph. $\bigcirc$ +2.0D. cyl. ax. 90°; O.S., +2.0D. sph. $\bigcirc$ +2.0D. cyl. ax. 87.5°). His visual acuity was 6/6 in each eye. With refractive correction there was no shift for distance; for near there were 3$^{\Delta}$ esophoria. He had good fusional amplitudes and 100-percent stereopsis (Keystone DB$_6$ card), in spite of the fact that there was a slight incomitance due, no doubt, to the asymmetric operation (primary position 3$^{\Delta}$ E, levoversion 10$^{\Delta}$ X, dextroversion 0).

The excellent result has been maintained. When he was last seen on May 27, 1957, the amplitude of fusion was even larger than before and the condition otherwise as found on previous visits. For distance there was no shift with correction, for near 4$^{\Delta}$ of esophoria. However, without correction the boy had an esotropia of 12$^{\Delta}$ for distance and 15$^{\Delta}$ for near.

Case 2

A six and one-half-year-old white girl, first seen on March 26, 1956, complained of diplopia of two weeks' duration. The mother had noted at the same time a turning of the left eye. There was no history of ocular difficulties prior to this episode. However, she had had frequent colds and tonsillitis throughout the winter, with some hearing loss, and an acute suppurative otitis media for which a myringotomy was done.

Except for a left esotropia, both eyes were normal in every respect. The uncorrected vision was 6/6, R.E., and 6/9—3, L.E. Without correction the angle of squint was about 25$^{\Delta}$ for distance and 45$^{\Delta}$ for near. An orthoptic check revealed normal retinal correspondence in all tests, some suppression, O.S., for distance and near in the Worth four-dot test, and small fusional amplitudes on the troposcope.

There was no evidence of a paralysis of the sixth nerve on either the right side or the left. Based on a noncycloplegic refraction, the child was given a correction of: O.D., +1.75D. sph. $\bigcirc$ −0.37 D. cyl. ax. 42°; O.S., +2.75D. sph.

She was seen again on August 3, 1956, at which time she reported that she still had diplopia off and on. With her correction the angle of squint was 16$^{\Delta}$ for distance and 25$^{\Delta}$ for near. Repeated re-examinations in October, November, and December, 1956, revealed an increase and instability of the angle of squint; DFP drops, and later a stronger correction for hypermetropia, based on refraction in atropine cycloplegia, were ordered in an attempt to minimize the accommodative factor and to stabilize the deviation.

This was achieved, and on February 2, 1957, the measurements were as follows: With glasses (O.D., +3.0D. sph.; O.S., +3.75D. sph.; DFP discontinued on November 23, 1956) 30$^{\Delta}$ for distance and 40$^{\Delta}$ for near; without glasses 60$^{\Delta}$ for distance, 80$^{\Delta}$ for near. The child now preferred the left eye for fixation and there was considerable suppression of the right eye in the Worth four-dot test both for distance and near vision. The diplopia had virtually disappeared by this time, but the retinal correspondence had remained normal. No fusional movements could be elicited on the troposcope.

The adduction was excessive in both eyes and it was decided to perform a recession of both medial rectus muscles. This was done on February 24, 1957. When examined again on April 2, 1957, it was found that the child had a vision of 6/6 in each eye with her correction; with glasses there was no shift in the prism and cover test either for distance or near. The patient still suppressed the right eye in the Worth four-dot test for distance, but fused in near fixation. On the troposcope the subjective and objective angle was at 12$^{\Delta}$ (proximal convergence), but there were fusional amplitudes of 14$^{\Delta}$ of convergence and 5$^{\Delta}$ of divergence. During April, 1957, the child was given a series of orthoptic treatments, followed by home exercises to reinforce her binocular co-operation.

When last seen on July 3, 1957, the child showed no shift for distance or near fixation with the glasses. Without glasses there was an esophoria of 6$^{\Delta}$ for distance and 12$^{\Delta}$ for near; there was fusion in distance and near vision on the Worth four-dot test; the fusional amplitudes, measured with rotary prisms, were 12$^{\Delta}$ of convergence and 4$^{\Delta}$ of divergence; N.P.C., measured objectively, nine cm.; measured subjectively with a red filter,[15] 12 cm.; 100-percent stereopsis with DB$_6$ Keystone card.

Case 3

This patient, a 14-year-old white girl, was seen at Washington University. On her first visit she complained of left esotropia and diplopia of six months' duration. The diplopia was intermittent for one week after which it became constant. Examination of the eyes revealed no abnormalities except for the strabismus. The vision was 20/20 in each eye with −5.5D. sph., O.U. Without correction there was a left esotropia of 50$^{\Delta}$ for distance, with correction 70$^{\Delta}$. The rotations were normal and there were no signs of a paralysis of an extraocular muscle. The orthoptic evaluation showed normal correspondence and fusional amplitudes with some alternating suppression. No systemic or neurologic abnormalities were found in a physical examination which included a spinal tap.

On October 23, 1956, a five-mm. recession of the left medial rectus muscle with a six-mm. resection of the left lateral rectus muscle was done. Postoperatively the patient demonstrated fusion

in all directions of gaze, with amplitudes of convergence up to 70Δ and divergence to zero. A slight incomitance was present in gaze to the left with overaction of the right medial and lag of the left lateral rectus muscles.

When the patient was last seen on May 27, 1957, she had 15Δ of esophoria for distance and 10Δ of esophoria for near.

CASE 4

This patient, a nine-year-old boy, was also seen at Washington University. On his first visit on May 29, 1957, he reported diplopia of four months' duration. The patient could date the onset of the diplopia to a baseball game where he was suddenly aware of two baseballs. His local ophthalmologist referred the patient for neurologic and ophthalmologic consultation.

There was no family history of strabismus or other disease. The patient had developed normally and had had no significant illness. There was no evidence of pathologic changes in the external, slitlamp, and ophthalmoscopic examination of the eyes. The intraocular pressure was normal and the visual fields were full. The visual acuity was 20/20 in each eye.

Investigation of the extraocular motility showed that the boy had a left esotropia of 30Δ in all directions of gaze except in levoversion where the deviation measured 34Δ. In the orthoptic analysis the patient had normal correspondence and amplitudes of fusion (15Δ convergence, 5Δ divergence, distance and near).

The patient was admitted for study to the Children's Neurologic Section at Children's Hospital for study. A re-examination of the eyes confirmed the previous findings. Neurologic consultation indicated partial left sixth nerve paralysis on the possible basis of nasal pharyngeal tumor with intracranial extension. However, this was not borne out by further studies. Electromyography proved both lateral rectus muscles to be normally functioning, without change in pattern in response to Tensilon. Electro-encephalograms showed a predominantly slow dysrythmia with overlying fast activity, indefinite in relation to complaints. Skull films and pneumoencephalograms were normal except for evidence of sphenoidal sinusitis.

Accordingly, treatment for the sinusitis was instituted. Surgery for the strabismus (bimedial recession) was recommended, but the operation was postponed at the request of the parents.

DISCUSSION

From a *practical* standpoint it is important to realize that an esotropic deviation with diplopia may arise at any age without being due to the paralysis of a lateral rectus muscle. It has been doubted in the past that this is possible (Morax, in his discussion with Terson[16]; Malbrán[17]), but the evidence for such an occurrence is incontrovertible. Furthermore, it is apparent from the literature and from the cases presented in this paper that a comitant esotropia of late and acute onset may present any of the earmarks of an esotropia beginning in infancy: it may be familial, accommodative, nonaccommodative, intermittent, constant, and occur in patients with widely varying refractive errors.

From a *theoretical* standpoint the cases with late onset of comitant esotropia gain particular significance, and it is of interest to inquire into the genesis of the deviation. The question arises: is the genesis essentially different in cases of late onset from the genesis in cases with onset in early infancy?

The answer to this question depends to some extent on one's beliefs about the etiology of comitant strabismus. If one takes the view that comitant strabismus is a condition which occurs in early infancy due to an abnormal development of the optomotor reflexes based on retarded myelogenesis (Keiner[18]) or due to a faulty development of the binocular reflexes (Chavasse) then a strabismus of late onset must necessarily have a different etiology. If one believes, however, that the normal sensorimotor cooperation of the eyes is the result of a delicate balance between the forces which tend to maintain this balance and the forces which tend to disrupt it,* as has been indicated in the discussion of the strabismus following artificial interruption of fusion, then it is

* Among the forces which work against the proper alignment of the eyes are: a large "basic" deviation (Swan[19]), weaknesses in the *anlage* of the sensory system (defective retinal rivalry and readiness to suppress; low responsiveness to disparate stimulation), particularly when combined with obtacles of optical nature (anisometropia, and so forth); abnormalities in the convergence and divergence innervation and in the relation of convergence and accommodation, either intrinsic or due to abnormal peripheral stimuli (uncorrected refractive errors, and so forth); mechanical and anatomic anomalies of muscles and orbits. They may also include a delayed development of the optomotor reflexes, as suggested by Keiner.

conceivable that this balance may be upset at any age.

We believe this latter more general view to be the correct one. The genesis of the strabismus of late onset would then be essentially the same as the genesis of the strabismus of early onset and there would be little reason to differentiate the cases in which the manifest deviation occurred following artificial interruption of fusion from those in which there is no such obvious cause for the appearance of the strabismus.

Whenever the proper alignment of the eyes has given way, there is nothing to prevent the forces tending to increase the deviation from becoming ever more active, and the diplopia-phobia postulated by van der Hoeve may well add its share to it.

While the genesis of the deviation is thus likely to be the same, regardless of the age at onset and of the immediate precipitating cause, the *course of the disease* is very much dependent on it. If the deviation occurs while the patient is in a highly plastic stage, in infancy or early childhood, there will be, indeed, an abnormal development of the binocular reflexes and all the well-known sensorimotor symptoms of strabismus will be found. At the same time, a functional cure will meet with considerable difficulties. On the other hand, the clinical signs and the course in a strabismus of late onset are easily explained on the basis of the fact that these patients have enjoyed more or less normal binocular vision prior to acquiring the manifest deviation. They all exhibit, therefore, normal retinal correspondence and frequently also good binocular co-operation when tested with a major amblyoscope. Once the proper alignment of the eyes is restored to the patients by nonsurgical or surgical means, they quickly regain full binocular cooperation. The diplopia accompanying the appearance of the deviation is no more surprising than is the diplopia occurring in patients with acute paralysis of an extraocular muscle.

III. Comitant convergent strabismus of the "Bielschowsky type"

Most authors recognize a third form of acute esotropia and refer to it as "Bielschowsky's type."

In 1922, Bielschowsky[20] reported on patients with acute comitant convergent strabismus of a special type which had previously been described by von Graefe[21] and others and who had these characteristics: myopic refractive error of 5.0D. or less; late, more or less acute onset of the deviation following physical or psychic shock or exhaustion; uncrossed diplopia for distance, fusion for near; no evidence of paralysis of the extraocular muscles; slight restriction of abduction, but no excess of adduction; neuropathic constitution.

Bielschowsky had no doubt that myopia played a role in the etiology of this form of strabismus. He accepted von Graefe's view that in uncorrected myopes there developed an increased tonus, a "dynamic preponderance" of the medial rectus muscles. This increased tonus was explained by the tendency of uncorrected myopes to hold print or sewing excessively close to the eyes and by the fact that the compensatory innervation—or relaxation of convergence—necessary to overcome the esophoria would be the less the nearer the habitual fixation distance in close work lay to the eyes. Ordinarily, the compensatory fusional (divergence) innervation would keep the increased tonus of the medial rectus muscles in check, but under adverse conditions it would not be able to do so, with a resulting manifest esotropia.

Von Graefe's description of the condition differed from Bielschowsky's only in that the former found an excessive adduction as well as a deficient adduction. Bielschowsky added the important observation that all patients in that category which he had observed showed signs of a neuropathic constitution, and he postulated furthermore a pre-existing esophoria and a generally excessive convergence tonus.

In the early literature, an excellent casuis-

tic contribution was given by Theobald[22] who summarized von Graefe's views clearly and succinctly and emphasized that the rarity of the occurrence was due to the fact that it depended upon the concatenation of circumstances seldom met with: uncorrected myopia, excessive close work, leading to "interni of more than average strength, with lateral rectus muscles preternaturally lengthened and weakened from constant stretching." His patient was a 39-year-old myopic dressmaker, who was also a constant reader, but who used glasses only for distance vision. She had had a convergent strabismus and annoying diplopia for some years; all signs corresponded to those already described. Successive tenotomies, first of the right medial rectus, then of the left, restored binocular vision.*

In the more recent literature there are only few references to cases of strabismus of this form. Cords[23] and Malbrán[24] mention it, but only report on the presentations of von Graefe and Bielschowsky whose opinions they share. Weber[25] has reported two cases in some detail and so has Franceschetti.[10] The cases described most recently by Dubois-Poulsen, Benmansour, and Attané[26] are of great interest in themselves, but do not seem to fit very well into this group.

In discussing the differential diagnosis of this type of strabismus, Bielschowsky, as well as Cords and Weber, mentions the fact that it has all the earmarks of a paralysis of divergence: uncrossed diplopia for distance; decrease in the distance of the double images as the fixation object approaches; single vision at one point at a certain distance from the eyes; no diplopia at near, or crossed diplopia if there is a secondary convergence insufficiency. Nevertheless, Bielschowsky and the authors following him did not believe that these cases belonged in the category of paralysis of divergence, because they felt that the diagnosis of a paralysis of divergence, while theoretically justified, was not supported by clinical and pathologic evidence, and because of the absence of signs of a severe central nervous disease in these patients.

Closer consideration shows, however, that there is no reason why cases of acute esotropia of the "Bielschowsky type" should not be identified with a paralysis of divergence. There is in these patients no excess of adduction, but a deficiency of abduction. The increased tonus of the convergence innervation and of the medial rectus muscles which has been postulated should lead to a convergence excess. In cases of convergence excess the distance of the double images increases instead of decreases when the fixation object is approached to the eyes and at no point is it seen singly.† Weber has also shown that while the patients possess good fusional amplitudes, as measured by rotary prisms, these are displaced relative to the zero point, that is, the amplitudes are on the convergence side and do not even reach zero. The patients then "lack relaxation," or, better, have no divergence amplitudes. Weber has also achieved good therapeutic results with the use of base-out prisms which is the treatment of choice for paralysis of divergences, whereas Bielschowsky felt that prisms were not indicated and advised instead bilateral advancement of the lateral rectus muscles.

Since Bielschowsky's publication in 1922, much has been learned about paralysis of divergence. It is clear from the literature and

* The following remark of Theobald's is of some interest. "The presence of annoying diplopia in a convergent strabismus of some years' standing struck me at once as anomalous (for I am a firm believer in the doctrine that amblyopia is soon produced in a squinting eye through active suppression of its retinal image); but the anomaly was explained, when it was discovered that *in reading the patient enjoyed binocular vision* (author's italics). In this way the retina of the squinting eye . . . was continually exercised. . . ." This was written in 1886. It sounds much more up to date than much that was published in the ensuing 40 or 50 years.

† Cases of acute esotropia in myopia of moderate degree with signs of convergence excess (increase in distance of double images when the fixation object approached) were described by Berlin[27] in 1897. He pointed out that this feature clearly separated his cases from those of von Graefe.

from our own experience that paresis or paralysis of divergence represents a definite clinical entity. It is also clear that it may occur in people without serious central nervous and systemic disease, although it has been recorded as a sequela of epidemic encephalitis, multiple sclerosis, pseudotumor cerebri and brain tumor, intracranial hemorrhage, head injury, lues, influenza, diphtheria, and lead poisoning.

It is conceivable that there may be an "organic" and a "functional" paralysis of divergence, just as there is an organic paralysis of convergence and a functional convergence insufficiency. Or else, the cause of the paralysis of divergence may remain subclinical in some cases and not detectable by our diagnostic methods. However this may be, paralysis of divergence is a definite clinical entity and its occurrence is not necessarily dependent upon severe neurologic or other systemic affections. Thus there would seem to be no reason why we should differentiate from it the cases of esotropia for distance in patients with myopia which have been reported as cases of acute strabismus of the "Bielschowsky type."

In concluding this paper we shall report an example of what we consider to be a typical, though mild, paralysis of divergence which occurred in an eight-year-old girl, the youngest patient in whom we have diagnosed this condition.

Case report

Case 5

The patient was first seen on February 28, 1956. Her presenting complaint was diplopia for distance which had begun acutely two weeks previously. She had had no headaches, fever, malaise, or any illness prior to or at the time of the onset of the diplopia, but she had had a few falls which, however, remained without consequence so far as the patient knew. Her local physician found her in excellent physical condition; a psychiatric examination was without any positive findings. She was referred to us by a member of the Department of Pediatrics, who could uncover no physical abnormality of any sort.

External examination, slitlamp examination, and funduscopy revealed no abnormality in either eye. The uncorrected vision was 6/6 in each eye, the refraction : O.D., +0.75D. sph.; O.S., +0.5D. sph. There was no observable shift in the cover test either for distance or for near, but there was homonymous diplopia at six m., the distance of the double images being about 10 to 12 cm. As the fixation object was approached to the eyes the double images approached each other and from three m. on there was no diplopia. On the troposcope the fusional amplitudes measured 26$^{\Delta}$ base-out and 4$^{\Delta}$ base-in; there was 60-percent single central binocular vision and 90-percent stereopsis; the N.P.C. was at four cm. There was no evidence of paralysis on the Lancaster red-green test.

With prisms of 2$^{\Delta}$ base-out in front of each eye the patient had single vision for all distances. She was given that correction and returned on March 22, 1956, reporting that she had worn the glasses with comfort and had experienced no diplopia when wearing them. She was asked to report again in six weeks but was not seen until November 11, 1956. At that time she informed us that she had had no illness of any sort since she had last been seen by us. She had experienced no diplopia while wearing the glasses, but the diplopia would return after she left the glasses off for 20 or 30 minutes. On examination it was found that with her glasses there was no diplopia, but after she had been without glasses for 35 minutes there was again spontaneous homonymous diplopia for distance, the separation of the double images being approximately eight cm. For near there was single vision. The patient was advised to wear the glasses if she felt the need for it and to come for a recheck in six months.

When last seen on June 14, 1957, the patient reported that she had discarded the glasses shortly after her visit to us in November, 1956, and that she had not seen double since. She had had no illness in the interim, had felt entirely well and had done very well in school. At this last visit she had no spontaneous diplopia; she had 90-percent single central binocular vision and 100-percent stereopsis; the fusional amplitudes had remained the same. With the Maddox rod there was an esophoria of 4$^{\Delta}$ to 5$^{\Delta}$ for distance and of 5$^{\Delta}$ to 6$^{\Delta}$ for near without refractive correction.

Summary

The three forms are described under which an acutely arising comitant esotropia may be observed.

It is concluded that the etiology of the acute esotropia following artificial interruption of binocular vision does not differ essentially from the etiology of the spontaneously occurring forms, except that in the former the precipitating cause is known.

It is furthermore concluded that comitant esotropia may arise at any age. Comitant eso-

tropia of late onset has no particular distinguishing features; all the well-known classes of comitant esotropia are represented. The diplopia accompanying it is an expression of the fact that the patient had binocular vision prior to the deviation; its explanation does not differ from that which applies to the diplopia in acute paralytic strabismus.

The genesis of a deviation appearing in older children and adults is likely to be identical with the genesis of a deviation manifesting itself in infancy, although additional factors may be present in the latter case. However, the course of the disease is materially influenced by the age of onset.

The cases of acute esotropia for distance with normal binocular vision for near seen in myopes and described by von Graefe, Bielschowsky, and others are clinically indistinguishable from cases of divergence paralysis. We could find no reason why they should be classified into a separate clinical entity.

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NOTE: While this paper was in print, an additional paper on convergent strabismus with acute onset came to our attention (Alajmo, A.: Arch. Ottal., **61**:217, 1957). The author points out, as we do, that the only distinguishing feature of this form of strabismus is the late onset and that it does not differ otherwise in its genesis or clinical picture from the convergent strabismus arising in early childhood.

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SPONTANEOUS INTRA-EPITHELIAL CYSTS OF IRIS AND CILIARY BODY WITH GLAUCOMA*

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Spontaneous intra-epithelial cysts of the iris and ciliary body have been described many times in the literature. For the most part the diagnosis has been suspected by observing a localized forward bulge of the iris[1-12] and/or a dark brown tumor presenting in the pupillary space, usually with the pupil dilated, but sometimes with the pupil small.[13-23]

François,[25] in 1948, was the first to report the observation by gonioscopy of cysts of the ciliary processes. In his case, after successful iridencleisis for acute glaucoma, by gonioscopic examination two cysts of the ciliary processes were observed in the coloboma. Except for two anterior synechias below, the angle was evidently of good width below and nasally. On the temporal side the angle was very narrow and the trabecular zone was not visible. Scheie,[12] in 1953, reported the diagnosis of cysts of the iris and ciliary processes by gonioscopic examination in 20 eyes of 16 patients. The presence of cysts was suspected in most cases by noting localized bulging in the periphery of the iris. In some cases, after finding cysts in one eye, examination of the other eye was carried out and cysts found in this eye also. The pupil was dilated widely and gonioscopic examination carried out, using the Koeppe contact lens, the microscope from a Comberg slitlamp, and a Barkan hand-lamp for illumination. Most of the cysts were on the ciliary processes, but some were evidently on the posterior surface of the iris. Some of the cysts were clear and transparent, whereas others were heavily pigmented. In some cases only one cyst was observed, in others several were seen, and in one case there were 12 cysts.

A heavily pigmented tumor mass presenting between the iris and lens led to a diagnosis of uveal sarcoma in several reported cases,[2, 4-6, 11, 16, 17] and the eye was enucleated. Pathologic examination of these eyes in each case revealed multiple cysts of the iris and ciliary processes. In the case reported by Bickerton and Clarke,[3] the tumor was removed by iridectomy and proved to be an iris cyst. In several other cases a diagnosis of iris cyst was made clinically, and the cyst removed by iridectomy.[7, 13, 14, 15, 19, 21-23] In a few cases a clinical diagnosis of iris cyst was made, but no operative treatment was carried out.[1, 8, 9, 18] Several authors have reported on the pathology of spontaneous epithelial cysts.[2, 4-7, 11, 14, 16-19, 21, 22, 24, 26]

In most of the reported cases there was no

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*From the Massachusetts Eye and Ear Infirmary.

impairment of the function of the eye, but glaucoma, or a history suggestive of glaucoma, has been noted in a few cases.[16, 17, 20, 25] Wintersteiner,[16] in 1906, reported the case of a 28-year-old man with a marked forward bulging of the iris in the lower outer quadrant of the right eye. When the pupil was dilated a dark-brown tumor was visible between the lens and iris. At a later examination the tension was said to be "slightly elevated." The patient complained of intermittent attacks of blurred vision and seeing colored haloes around lights. The eye was ultimately enucleated, and on pathologic examination multiple cysts of the iris and ciliary processes were noted.

Pagenstecher,[17] in 1910, reported the case of a patient who gave a history of intermittent severe pain the right eye. A marked forward bulge of the iris in the lower outer quadrant was noted. With the pupil in middilatation, a dark-brown mass could be seen projecting out from behind the iris one mm. beyond the pupillary border. Malignant melanoma was suspected and the eye was enucleated. Pathologic examination revealed multiple cysts of the iris and ciliary body. Although prior to enucleation the tension was never actually found elevated, the history of intermittent pain was strongly suggestive of glaucoma.

Vogt,[20] in 1921, reported that he had observed four cases in which multiple cysts were visible in the pupillary area. Glaucoma was present in all four cases, but was controlled by miotics. He made no note of the depth of the anterior chamber. One cannot determine from his report whether or not the glaucoma was primary or was secondary to angle closure from multiple cysts.

In François'[25] case acute glaucoma was present prior to operation. Postoperatively gonioscopy revealed two peripheral anterior synechias below, and the entire temporal angle was extremely narrow, so that the trabecular zone was not visible. The angle was evidently of average width elsewhere. This description is suggestive of the presence of multiple cysts on the temporal side, at least, which may have been responsible for the extreme narrowing of the angle leading to acute glaucoma.

Aside from François'[25] case we have not found in the literature any description of the gonioscopic appearance of the chamber angle in cases of multiple spontaneous cysts of the iris and ciliary processes.

The purpose of this communication is to report on three eyes in three patients in which acute glaucoma was evidently caused by closure of the angle from forward bulging of the periphery of the iris due to multiple cysts of the iris and ciliary processes. A fourth case is reported of multiple cysts of the iris and ciliary body in which the chamber angle was excessively narrow in one eye without increase in tension or history suggesting glaucoma.

Case reports

Case 1

A woman, aged 41 years, was first seen in the clinic of the Massachusetts Eye and Ear Infirmary May 22, 1945. She was then 29 years of age. There was a history of intermittent pain and blurred vision in the left eye for four years. Examination revealed vision of 20/20 in each eye. Media were clear, fundi normal. It was noted that the anterior chambers were shallow. Tension was: R.E., 19; L.E., 42 mm. Hg (Schiøtz). Pilocarpine (one percent, four times a day) was prescribed for the left eye.

On May 29, 1945, tension was: R.E., 18 mm. Hg; L.E., 20 mm. Hg. Iridectomy was advised for left eye.

On May 31, 1945, a basal iridectomy was performed on the left eye. Convalescence was uneventful and the patient was discharged June 6, 1945.

On July 17, 1945, tension was: R.E., 20 mm. Hg; L.E., 24 mm. Hg. The patient was then followed by her local ophthalmologist. She returned to the clinic March 19, 1946. Tension was: R.E., 24 mm. Hg; L.E., 37 mm. Hg; Pilocarpine (two percent, four times a day) and eserine ointment at bedtime were prescribed.

On April 2, 1946, tension was: R.E., 24 mm. Hg; L.E., 30 mm. Hg. During the next eight years the patient was seen regularly by her local ophthalmologist. A miotic was used continuously in the left eye. Tension was well controlled until May 19, 1954, when that in the left eye was found to be 40 mm. Hg. She was referred to one of us (P. A. C.) in consultation.

Examination on June 4, 1954, revealed vision of 20/20 in the right eye, and 20/30+ in the left

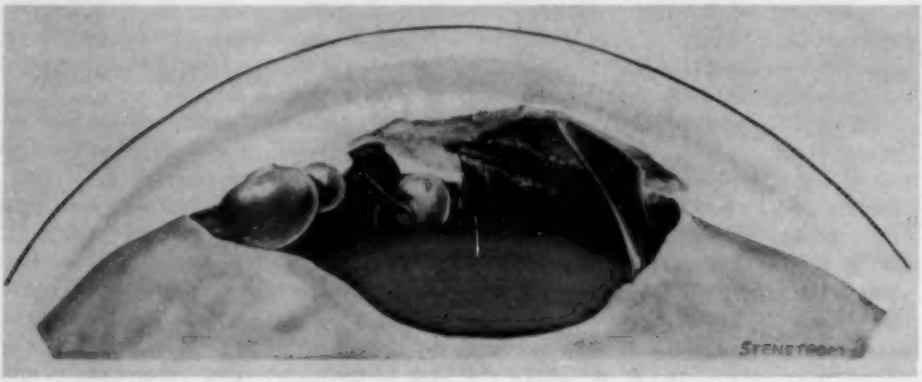

Fig. 1 (Chandler and Braconier). Drawing from a stereogoniophotograph, showing cysts of the ciliary processes in the coloboma.

eye. Fields were full, blindspots normal. Media were clear, fundi normal. Tension was: R.E., 17 mm. Hg; L.E., 40 mm. Hg. In the right eye there was a pronounced forward bulge of the iris above where it seemed to touch the cornea. There was a smaller bulge nasally. Gonioscopy* revealed that the iris was in contact with the cornea above. The angle appeared closed from the 11- to 3-o'clock positions. From the 3- to 6-o'clock positions, the angle was open and one could see the scleral spur. There was a small area of closure at the 6-o'clock position. From the 6- to 9-o'clock positions, the angle was narrow but open. At the 9-o'clock position, the iris bulged forward and the angle was closed, or nearly so. At the 10-o'clock position there was a small area of open angle. From the 10- to 11-o'clock positions, the angle was very narrow but probably open.

In the left eye a little of the trabecular zone seemed to be free. Otherwise the angle appeared to be completely closed. There was a forward bulge of the peripheral iris at the 2-o'clock position where it was in contact with clear cornea. The iridectomy was seen to be basal. In the coloboma four small cysts of the ciliary processes were noted (fig. 1). One cyst was heavily pigmented. The others were transparent with only a few flecks of pigment on them. D.F.P. (0.1 percent twice a day) and epinephrine bitartrate (one percent, three times a day) were prescribed for the left eye. On June 8, 1954, tension was: R.E., 22 mm. Hg; L.E., 17 mm. Hg.

On August 30, 1954, the patient was admitted to the Massachusetts Eye and Ear Infirmary. When the pupil of the right eye was dilated a dark brown cyst could be seen above, projecting slightly beyond the pupillary border. A cyst could also be seen behind the iris at the 9- and 5-o'clock positions. A basal iridectomy above was done on the right eye on September 4, 1954.

During the hospital stay various miotics were tried on the left eye. With DFP (0.1 percent twice a day) and epinephrine bitartrate (one percent twice a day) tension ranged from 25 to 30 mm. Hg.

The patient was discharged September 9, 1954. She was seen in the clinic periodically until February, 1955. Tension was in the normal range in both eyes at all visits. Since then the patient has been followed by the local ophthalmologist. He reported on November 15, 1957, that the tension in both eyes has been 25 mm. Hg or less on all examinations. The patient has used four-percent pilocarpine three times a day and 0.05-percent DFP once a day in both eyes.

Case 2

A man, aged 54 years, was first examined by one of us (P. A. C.) on January 19, 1955. There was a history of blurred vision and pain in the left eye in November, 1950, which cleared up without treatment. Mild attacks of a similar nature continued to occur from time to time until a severe acute attack of glaucoma developed in December, 1954. The patient consulted an ophthalmologist who found a typical picture of acute glaucoma in the left eye with a tension of 90 mm. Hg (Schiøtz). Treatment with four-percent pilocarpine and Diamox quickly brought the tension to normal.

Examination on January 19, 1955, revealed the vision of both eyes to be 20/30 with correction. Media were clear, fundi normal. In the right eye the pupil was round and central, three mm. in size, and reacted normally. The anterior chamber appeared shallow overall. No note was made at this time in regard to localized peripheral bulges in the iris on slitlamp examination. Tension was 17 mm. Hg (Schiøtz). Gonioscopic examination showed the angle to be wide and open nasally from the 12- to 5-o'clock positions, with a broad ciliary band visible. The trabecular zone was heavily pigmented.

* In all cases reported gonioscopy was done using the Koeppe contact glass, a microscope from a slitlamp, and a Barkan hand-light for illumination.

At the 5-o'clock position, the angle was much more narrow, and between the 6- and 8-o'clock positions, the angle was excessively narrow, with a pronounced forward bulge of the iris in the periphery in this region. Between the 8- and 10-o'clock positions, the angle was wider, so that the scleral spur could be seen. From the 10- to 11:30-o'clock positions, the angle again appeared excessively narrow.

In the left eye the anterior chamber appeared extremely shallow. The pupil was 3.5 by 4.5 mm. and showed no reaction to light. On slitlamp examination the iris appeared to be in contact with the cornea below and temporally. Gonioscopic examination showed the angle to be extremely narrow but open from the 12- to 6-o'clock positions. From the 6- to 9-o'clock positions, the angle was closed. From the 9- to 10-o'clock positions, the angle was very narrow but open. It appeared closed from the 10- to 12-o'clock positions.

The right pupil was dilated widely with homatropine and neosynephrine. Gonioscopic examination was again carried out. Below and temporally a large dark-brown iris cyst presented between the lens and iris. It projected slightly beyond the pupillary border. On either side of this cyst where the iris was held away from the lens, a continuous row of cysts of the ciliary processes was seen. Most of the lower angle appeared closed.

The patient was admitted to the hospital and, on January 20, 1955, a peripheral iridectomy was done in the 1:30-o'clock position on the left eye. On January 22nd, an operation was performed on the right eye with the pupil widely dilated. Under topical anesthesia a small knife needle was passed through the cornea at the limbus in the 9-o'clock position, and the iris cyst in the 7-o'clock position was punctured.

On January 25, 1955, gonioscopy with dilated pupils was again carried out on both eyes. In the right eye, in the region of the cyst which was punctured, dark-brown material covered the ciliary processes, presumably the collapsed cyst. In the region of the 6-o'clock position two iris cysts could be seen which did not quite reach the pupillary border (fig. 2). The angle, though somewhat narrow in places, was everywhere open except for one small area at the 6-o'clock position. This represented a considerable improvement in the state of the angle with the dilated pupil as compared to that noted before puncture of the large iris cyst.

In the left eye the angle was narrow but open on the sides. It appeared closed above and below. One small cyst on a ciliary process could be seen through the operative coloboma. Below, two cysts were noted on the posterior surface of the iris which did not reach the pupillary border. On either side of these cysts, as far as the iris was held away from the lens, a continuous row of cysts of the ciliary processes could be seen. The patient was discharged from the hospital on January 25, 1955.

During the next several months the patient was examined from time to time. No treatment was employed. Tension was always below 20 mm. Hg in the right eye, 20 to 25 mm. Hg in the left. On March 12, 1956, tension was: R.E., 20 mm. Hg; L.E., 27 mm. Hg.

Gonioscopy was carried out on both eyes. In the right eye the appearance was unchanged from the last examination. In the left eye, from the operative coloboma to the 3-o'clock position, the angle was open and of fair width. From the 4- to 8-o'clock positions, the angle was excessively narrow or closed. There was a small area of apparent closure at the 9-o'clock and another at the 10-o'clock position. Otherwise, the angle appeared open and of fairly good width from the 8-o'clock position around

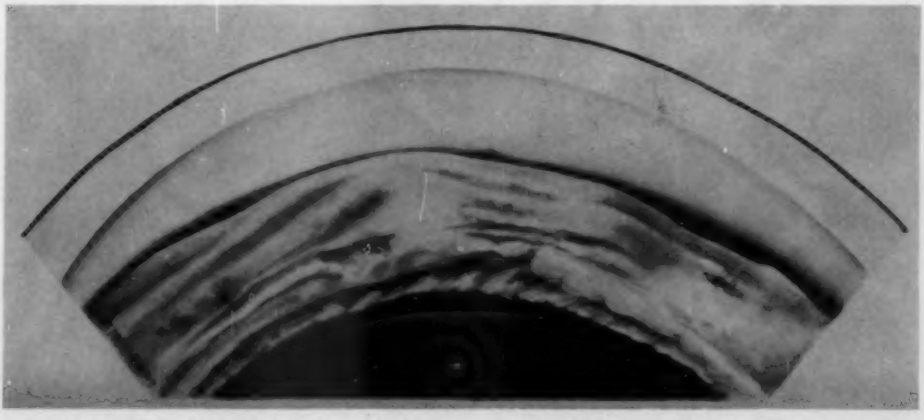

Fig. 2 (Chandler and Braconier). Drawing from a stereogoniophotograph. The iris cysts cannot be seen in the photograph or drawing but note that the iris is held away from the lens between the 5-o'clock and 7-o'clock positions.

to the coloboma. With the dilated pupil, a large iris cyst could be seen between the 3:30- and 5-o'clock positions, which just reached the pupillary border. As noted before, on either side of this iris cyst a continuous row of cysts of the ciliary processes could be seen in the area where the iris was lifted away from the lens.

On March 14, 1956, the iris cyst between the 3:30- and 5-o'clock positions was punctured with a small knife-needle.

When the right eye was examined goniosocopically with the pupil dilated, there was no sign of recurrence of the iris cyst which had been punctured on January 22, 1955. Re-examination in September 1957 revealed no recurrence of the cyst.

CASE 3

A man aged 53 years, was first seen by one of us (H. E. B.) on April 10, 1956. The history revealed that about one month ago the patient experienced a temporary episode of blurred vision in the right eye with pain and redness lasting two or three hours. Five days ago he experienced another similar attack in the right eye. Between these two episodes he had experienced two or three mild attacks.

Examination on April 10, 1956, revealed the vision to be 20/20 with correction in each eye. Fields were normal in the left eye. Media were clear and the fundus normal. The anterior chamber was clear and of normal depth. Slitlamp examination revealed localized radial bulges in the iris at the 4-, 6-, and 7-o'clock positions. The pupil was slightly ovoid with a heavy ectopic pigment border, thinnest in the lower temporal quadrant.

Gonioscopic examination revealed a mild convexity of the iris. The radial humps flattened out toward the angle which appeared to be open throughout. Tension was 23 mm. Hg (Schiøtz). The pupil was then dilated and gonioscopic examination again carried out. From the 12- to 2-o'clock positions, the angle was of good width. At the 2-o'clock position, there was a slight localized bulge, which made the angle here extremely narrow. There was another bulge at the 3-o'clock position where the angle may have been closed. At the 6-o'clock position there was a radial bulge which did not reach the periphery. The angle was of good width clockwise to the 10-o'clock position. From the 10- to 2-o'clock positions, the iris, almost, if not quite, touched the cornea. There was then a small open area, very narrow, followed by a localized bulge where the iris again practically touched the cornea. There was an appreciable space between the lens and the iris on the temporal side from the 1- to 6-o'clock positions. In this region the iris was held off the lens by a thin layer of dark-brown tissue projecting slightly beyond the pupillary border. This extended to the 8-o'clock position (fig. 3). At the 9-o'clock area, the iris was held off the lens by a brownish mass filling the space between the lens and iris, much like the cyst at the 6-o'clock position. The whole mass between the 9-o'clock and 8-o'clock positions appeared to be continuous with he localized bulge below.

Examination of the right eye showed the media to be clear and fundus normal. There was a brown cystlike mass projecting from behind the pupillary border at the 12-o'clock position and extending to the 2:30-o'clock position in the upper nasal quadrant. A trilobulated smaller mass extended from approximately the 4-o'clock position temporally around to the 10-o'clock position. A smaller lobe extended from the 10:30- to 11:30-o'clock position. The lobes were of about equal size but the more temporal one extended further into the pupillary area (fig. 4). The stroma of the iris was normal. The pupil appeared to roll over these masses on contraction and roll back on dilation. The masses moved to a lesser degree over the lens.

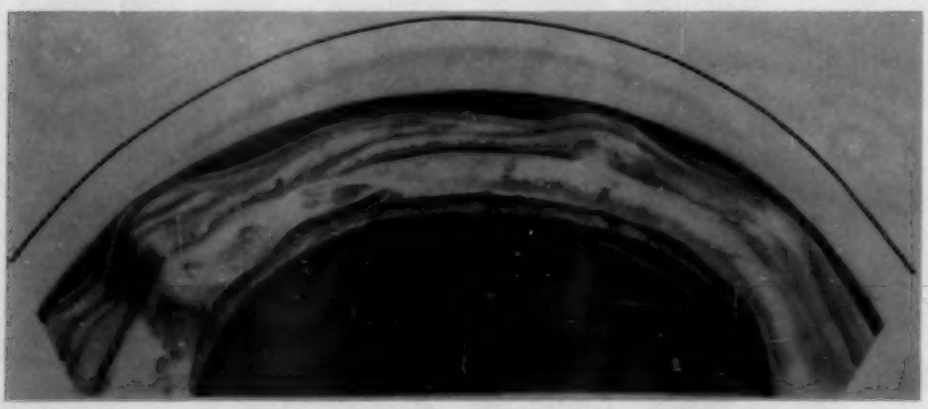

Fig. 3 (Chandler and Braconier). Drawing from a stereogoniophotograph, showing a cyst presenting between the iris and lens, between the 6-o'clock and 8-o'clock positions, and localized bulges in the periphery of the iris.

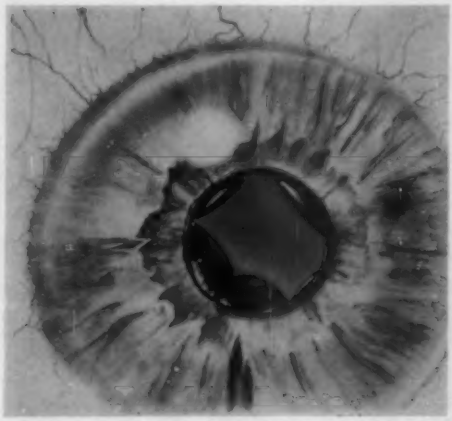

Fig. 4 (Chandler and Braconier). Drawing from a stereophotograph, showing cysts projecting beyond the pupillary border.

On slitlamp examination it could be seen that the iris diaphragm was elevated above the lens by the protruding masses, making the anterior chamber more shallow than that of the left eye. The masses and lobulations were smoothly rounded, covered with a brown homogenous pigmentation.

Gonioscopic examination revealed the iris to be elevated from the lens with a marked convexity. The angle was quite variable in width. The upper temporal and upper nasal areas were definitely capable of closure; whereas, other areas inferiorly did not appear capable of closure. The tension was 27 mm. Hg (Schiøtz) and because of the history it was not considered safe to dilate the pupil for further gonioscopic examination.

On April 11, 1956, an operation was performed on the right eye. A knife-needle was passed through the periphery of the cornea at the 1-o'clock position into the anterior chamber and taken to the lower temporal cysts which lay beneath the pupillary margin. Both of these cysts were punctured and were seen to collapse. As a matter of fact, when the more temporal one was punctured, the inferior one collapsed. The needle was withdrawn and a gonioscopic lens was placed on the eye.

The angle appeared much deeper. The iris lay flat against the lens where previously it was lifted off the lens. The knife-needle was passed into the anterior chamber through the lower temporal periphery of the cornea, across to the upper temporal and upper nasal cysts. These were both punctured and both collapsed and again the iris flattened out. The needle was withdrawn and the gonioscopic lens was again applied. As before, the iris had flattened out but the angle in this area was still quite narrow. A basal iridectomy was then done extending from the 10:30- to 1:30-o'clock positions. Convalescence was uneventful. The pathology report was cyst of the pigment epithelium of the iris.

The patient was re-examined on October 27, 1956. The left eye was as previously described.

The right eye was white and quiet. The posterior pigment layer of the cyst could still be seen temporally and nasally at the periphery of the iris pillars. The lens was clear and the fundus normal.

By gonioscopy the angle appeared closed for one hour of the clock, clockwise from the nasal border of the coloboma and then appeared open and fairly uniform in width clockwise to about the 9-o'clock position. Here it became quite narrow but was probably open to the 10-o'clock position. From the 10-o'clock position up to the edge of the coloboma, the angle appeared closed. In the coloboma there was a patch of dark-brown pigment material covering the base of the ciliary processes from the temporal border of the coloboma to within one mm. of the

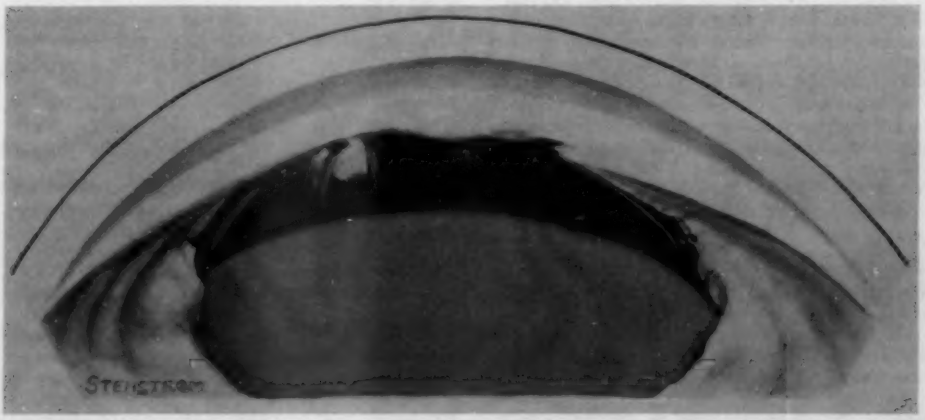

Fig. 5 (Chandler and Braconier). Drawing from a stereogoniophotograph, showing pigmented material covering the ciliary processes. On the right-hand border of the coloboma, the edge of a cyst is visible.

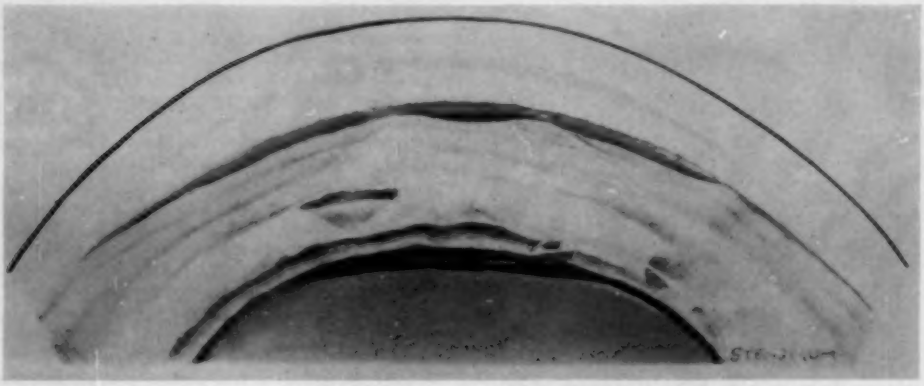

Fig. 6 (Chandler and Braconier). Drawing from a stereogoniophotograph, showing the remains of a collapsed cyst between the 6-o'clock and 8-o'clock positions.

nasal border of the coloboma.

At the nasal border of the coloboma there was a dark-brown cyst covering the base of the ciliary processes. There was a patch of brownish tissue running from the base of the coloboma behind the iris for one hour of the clock. This projected slightly beyond the iris rim (fig. 5). On the back surface were two round, bullous masses. From here clockwise to the 4-o'clock position, the iris was in close approximation to the lens. From the 4-o'clock to the 5:30-o'clock position, there was some brownish tissue just visible beyond the pupillary border which held the iris slightly above the lens surface. From the 6- to 8-o'clock positions, there was another such mass. This probably represents the remains of the collapsed cyst (fig. 6). At the 10-o'clock position, under the iris, were two round cysts which appeared to be attached to the back of the iris.

The patient was seen four months later, February, 1957. He had experienced some discomfort of the left eye at that time. However, examination revealed the condition of both eyes to be unchanged and the tension was well within normal limits.

A six months' check-up on August 10, 1957, revealed no recurrence of cysts and no new cyst formation. The patient was having no discomfort and visual acuity in each eye was 20/20 with correction. The tension was 17 mm. Hg (Schiøtz) in each eye.

CASE 4

A woman aged 54 years, was first examined October 31, 1956. There was a history of failing vision in the left eye for two or three years. In the right eye the anterior chamber was normal, pupil round and active, media clear, fundus normal. Tension was 27 mm. Hg (Schiøtz).

Slitlamp examination revealed a considerable number of pigment granules on the posterior corneal surface. Gonioscopic examination revealed a localized peripheral bulge in the iris between the 1:30- and 2-o'clock positions where the angle was quite narrow but open. From this area clockwise to the 8-o'clock position, the angle was wide, with a visible ciliary band. There was a peripheral iris bulge at the 8-o'clock position, with marked narrowing of the angle. There were other small bulges at the 9- and 11-o'clock positions. The filtration meshwork showed a very heavy deposit of pigment throughout, similar to that which is seen in so-called pigmentary glaucoma.

In the left eye the anterior chamber was shallow, the pupil round and active. There was a mature cataract. Light projection was accurate. Tension was 20 mm. Hg (Schiøtz).

Slitlamp examination revealed a number of pigment granules on the posterior corneal surface. Gonioscopic examination revealed the angle to be open throughout. It was excessively narrow clockwise from the 11- to the 5-o'clock positions. From the 5- to 8-o'clock positions, the angle was somewhat wider but the ciliary band was not visible. At the 8-o'clock position, there was an excessively narrow area possibly closed. From the 8- to 11-o'clock position, the angle was much wider with the ciliary band visible. The meshwork was heavily pigmented throughout.

Tonography showed diminished outflow in the right eye, normal in the left.

On December 16, 1956, an intracapsular cataract extraction with full iridectomy was done on the left eye. Convalescence was uneventful.

On February 1, 1957, gonioscopy was done with the pupils widely dilated.

The right eye showed the iris to be in contact with the lens from the 11-o'clock position clockwise to the 5-o'clock position. At the 5-o'clock position, the iris began to lift away from the lens, so that from about the 5:30- to 10-o'clock positions, it was possible to see between the iris and lens. A continuous row of cysts on the ciliary processes was observed. Some showed very little pigment, others were heavily pigmented. At the 9-o'clock

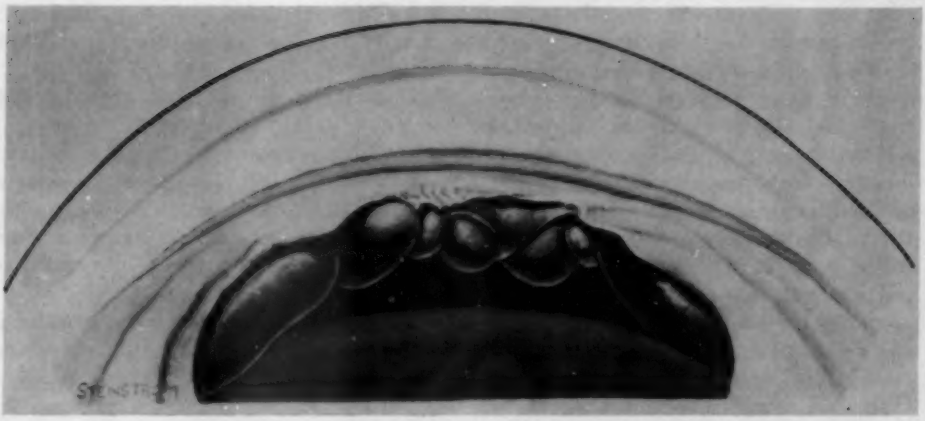

Fig. 7 (Chandler and Braconier). Drawing from a stereogoniophotograph, showing the continuous row of cysts of the ciliary processes with an iris cyst between the 2-o'clock and 3-o'clock positions.

position, one cyst came close to the pupillary border. This was probaby an iris cyst.

Left eye. Due to the absence of the lens it was possible to see very clearly the area behind the iris throughout the entire circumference. There was a continuous row of cysts all the way around, each one touching, or almost touching, the next (fig. 7). For the most part they were cysts of the ciliary processes. There was one iris cyst between the 2- and 3-o'clock positions. The angle was generally wider than preoperatively, but still fairly narrow in some portions.

Discussion

In the first three cases typical acute angle-closure glaucoma occurred. There were prodromal episodes during the month preceding the severe attack in Case 3. In Case 1, basal iridectomy was successful and tension remained normal with miotic treatment for eight years. The fact that, after this long period, tension rose to 40 mm. Hg is a most unusual finding. As a rule in acute glaucoma, if iridectomy is done in time, a large part or all of the angle opens and there is permanent control of the glaucoma. A search for the cause of this most unusual late rise in tension led to the diagnosis of multiple cysts. There is no record of the state of the angle at the time of iridectomy in this case, but it must have opened in large part and remained open, else the tension would not have stayed in the normal range for so long a period. The rise in tension eight years after iridectomy, in spite of miotic treatment, was obviously due to closure of the angle, presumably due to gradual enlargement of the cysts behind the iris. The discovery of multiple cysts in this eye led to a careful examination of the right eye and the finding of multiple cysts.

In Case 2 the acute attack in the left eye was controlled medically, and at the time of our first examination the gonioscopic picture was quite typical of what one usually sees in the angle when the tension has been controlled medically after an acute attack of angle-closure glaucoma. The angle was excessively narrow throughout, probably closed in some areas. It was the gonioscopic picture in the fellow right eye which led to the suspicion of multiple cysts later confirmed when the pupils were dilated. In this eye, in places the angle was of normal width with ciliary band readily visible. In other areas, due to a marked forward bulging of the iris, the angle was excessively narrow, almost closed. Such an appearance is never seen in the fellow uninvolved eye in cases of primary angle closure glaucoma. In such fellow eyes one finds the angle to be uniformly excessively narrow.

In Case 3, even with a normal pupil, iris

cysts were visible at or beyond the pupillary border and the diagnosis was readily made.

In Case 4 the angle in the left eye was excessively narrow throughout except between the 8- and 11-o'clock positions, so that one felt that acute glaucoma might easily have been provoked by mydriasis. The unevenness of depth of the angle in the fellow eye and the localized peripheral bulging of the iris led to the suspicion of cysts. After lens extraction on the left eye it was possible gonioscopically to visualize clearly the area behind the iris in the entire circumference. It could be seen that there was a continuous row of cysts, one touching the other all the way round. This would explain the uniform narrowing of the angle preoperatively.

It seems probable in all three eyes which had a fairly uniform narrowing of the entire angle and developed acute glaucoma, that the cysts were continuous all the way round. Only where iris cysts are present, or there is an unusually large ciliary body cyst, is the iris held away from the lens sufficiently to permit gonioscopic examination of the area behind the iris root.

In each case where the iris was held away from the lens by an iris cyst, or a large ciliary body cyst, it was possible to see on either side other iris or ciliary body cysts. Thus in the reported cases in which a large iris cyst was diagnosed as malignant melanoma and the eye enucleated, it seems probable that gonioscopic examination would have revealed multiple cysts and the correct diagnosis would have been made.

Iris cysts are always heavily pigmented. Ciliary body cysts may be as heavily pigmented as iris cysts, may show only scattered flecks of pigment, or may be completely transparent. A striking feature in all the cases here reported was the heavy pigmentation of the trabecular meshwork similar to that seen in pigmentary glaucoma. Since most of the cysts are heavily pigmented one suspects that the cysts may be the source of the heavy pigmentation of the meshwork. This pigmentation itself may possibly lead to glaucoma even though the angle remains open. In the right eye of Case 4 a diagnosis of early open-angle glaucoma was established by tonography.

Once the diagnosis is established, what treatment should be employed? In cases in which acute glaucoma develops, iridectomy is indicated. Probably broad basal iridectomy is preferable to peripheral iridectomy since it is sometimes possible to remove a large iris cyst with the iridectomy. This protects at least this portion of the angle.

What should be done about the remaining cysts which threaten further closure of the angle and a return of the glaucoma? In Cases 2 and 3 simple puncture of iris cysts resulted in a widening of this portion of the angle, and the cysts had not reformed, in one case nine months and in the other one and one-half years later. If the larger cysts reform, periodic puncture could be carried out as a palliative measure.

Puncture of iris cysts which reach the pupillary border or beyond can be safely done. It occurred to us that it might be made easier by operating with the aid of a contact lens. It does not seem feasible to puncture ciliary body cysts by passing a knife between the iris and lens since the space is so narrow there would be great risk of injuring the lens. In cases where such cysts produce a pronounced peripheral bulge of the iris it would appear to be a safe procedure to puncture them through the iris, but we have not yet attempted this. A filtering operation would be a logical procedure if the glaucoma cannot be controlled in any other way.

The diagnosis of multiple cysts in cases of acute glaucoma is important from the standpoint of prognosis. In the ordinary case of acute glaucoma, if iridectomy is done in time, one expects complete and permanent relief of the glaucoma. If multiple cysts are present a more careful follow-up is indicated in anticipation of a return of elevated tension from further angle closure as a result of continued growth of cysts.

In routine slitlamp examination, if one scans the entire iris, it is often possible to note localized areas where the iris bulges

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forward or that the anterior chamber is more shallow on one side than on the other. In such a case wide dilatation of the pupil and gonioscopic examination should be carried out. However, if the entire angle is very narrow, and especially if acute glaucoma has occurred or is suspected from the history, dilatation of the pupil must be deferred until after iridectomy. In such cases dilatation of the pupil of the fellow eye and gonioscopic examination may establish the diagnosis, as in Cases 2 and 3.

In Case 4 cysts were suspected on account of the localized peripheral bulging of the iris in the right eye. The angle was so narrow in the left eye it was feared that dilatation of the pupil might precipitate acute glaucoma. Gonioscopy with dilated pupils was therefore deferred until after cataract extraction on the left eye. Then both eyes were examined with dilated pupils and the diagnosis was obvious.

We have observed several cases showing single cysts of a ciliary process. The finding of a localized peripheral bulge in the iris on slitlamp examination led to the suspicion of cyst, and the diagnosis was confirmed by gonioscopy with dilated pupil. In one case on slitlamp examination the angle appeared to be strikingly more narrow on the temporal side of both eyes than on the nasal side. Gonioscopy revealed a very narrow angle temporally and a wide angle nasally. Gonioscopy with dilated pupils revealed multiple cysts of the ciliary processes on the temporal side in each eye. This patient will be followed more closely on account of the possibility of ultimate closure of the temporal angle and glaucoma.

Summary

The literature is reviewed and four cases of multiple cysts of the iris and ciliary body are reported, three of which had acute angle-closure glaucoma. The presence of such cysts is suggested by observing uneveness in the depth of the anterior chamber and especially localized forward bulging of the iris. Gonioscopic examination is the most valuable diagnostic method. Great variation in the width of the chamber angle is very suggestive of the presence of cysts. With the pupil dilated, cysts of the iris and ciliary body are readily visible in the areas where the iris is held away from the lens by a cyst. In the case of large iris cysts which project beyond the pupillary border a mistaken diagnosis of malignant melanoma can be avoided by observing other cysts of the iris or ciliary body on gonioscopic examination. In the case of multiple cysts, their continued growth results in a marked narrowing of the chamber angle leading to acute glaucoma. If acute angle-closure glaucoma develops, iridectomy is indicated, just as in primary glaucoma. It is suggested that puncture of the larger cysts may be employed as a palliative measure to prevent further angle closure. In cases of multiple cysts with acute glaucoma, the prognosis must be more guarded after operation on account of the possibility of further closure from continued growth of the cysts. A heavy deposition of pigment in the corneoscleral meshwork is a characteristic feature and may itself ultimately lead to glaucoma even without closure of the angle.

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Explanation of references

Localized peripheral bulge of the iris [1–10]
Presenting in the pupil [11–20]
Enucleation for malignant melanoma [3–6, 11, 16, 17]
Diagnosis of iris cyst made clinically, removed by iridectomy [7, 12, 14, 18, 19, 21–23]
Diagnosis of cyst made clinically, no operation [1, 8, 9, 15]
Pathology [2, 4–7, 13, 14, 16, 17–18, 21, 23, 24, 29]
Glaucoma noted or suspected from history [16, 17, 20, 23]

ments mask the finer labyrinthine effects the environment. As this resolved the patient ob-

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SOME OBJECTIVE AND SUBJECTIVE OBSERVATIONS ON THE VESTIBULO-OCULAR SYSTEM*

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That the vestibular apparatus, and particularly the labyrinths, plays an important role in the control of ocular movements is taken for granted. The violent nystagmus and illusory movement of the environment that occur with diseases of the peripheral labyrinth dramatically attest to this. Moreover, this control can be quantitatively documented under normal conditions with varying degrees of acceleration and deceleration (Graybiel[1]). Yet, with rare exception (Ford and Walsh[2]), there appears to be little appreciation of the essentiality of this labyrinthine control in stabilizing the eyes during small, seemingly trivial, movements of the head.

The voluntary and opticokinetic move-

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ments mask the finer labyrinthine effects under normal conditions and few persons interested in ocular movements have had the opportunity—or misfortune—to study them subjectively from a pathologic point of view. A notable exception to this is the case of Crawford who described, with admirable clarity, the symptoms of his own loss of labyrinthine function following an overdosage of streptomycin.[8] It was my contact with Dr. Crawford on several occasions and a personal encounter with what was called "labyrinthitis" that prompted my immediate interest in the visual phenomena associated with labyrinthine disturbances and emphasized to me the important role the semicircular canals play in what are ordinarily considered minor activities of visuospatial orientation. It is the purpose of this report to point out some of these observations and to present a few other phenomena not generally recognized. This will be done through a description of two cases and an analysis of my own symptoms.

Case reports

Case 1

M. M. (12-62-29) was a 48-year-old nurse who was given a total of 21 gm. of streptomycin over a 12-day period for tuberculosis of one kidney. After receiving approximately 16 gm., she developed vertigo that increased over a period of several days to the point that she was unable to turn over in bed. In the meantime, she had had a nephrectomy and her symptoms were at first attributed to a postoperative disturbance. The streptomycin was therefore continued for several days after the onset of the vertigo.

The vertigo continued to be relatively severe for about one week. It was acutely aggravated by movements of the head and was initially accompanied by moderate vomiting and illusory rotation of the environment. In the subsequent two months it gradually improved. The patient has been followed a total of five months since the onset of the vertigo with little subjective change in the past three months.

Two weeks after the onset, no nystagmus could be elicited by irrigation of either ear with ice water. Five months after the onset there was still no vestibular function that could be detected by rotation with a Bárány chair.

The patient's visual disturbances constituted a conspicuous part of her symptoms from the start. At first there was a violent illusory rotation of the environment. As this resolved the patient observed that she was unable to see clearly when her body was in motion. Specifically the environment appeared to oscillate up and down while she walked or as she rode in a car. This was, and has continued to be, so severe that she is unable to recognize people along the street unless she stops and remains immobile for a second or two. There has been only slight spontaneous improvement in this symptom but there is considerable symptomatic improvement on wearing a Thomas collar or holding her head rigid between her hands as she walks. In contrast to the up and down oscillations, no horizontal oscillations have been noted at any time.

Reading was at first difficult. The lines of print ran together and drifted up and down unless her head were supported or unless she was able to lean it against a rigid support. Fatigue always made the reading more difficult. Reading on a train has been impossible. This difficulty in reading has improved considerably with time but is still present, one year after the onset, when the patient is fatigued.

Examination of the eyes five months after the onset of the vertigo revealed little objective abnormality. Ocular movements were full without dissociation, dysmetria, or nystagmus. So long as the patient's head was motionless she could exercise full gaze movements in all directions without untoward symptoms. The opticokinetic response was normal and symmetric.

The patient's visual acuity was 20/15 as long as she was immobile. Jogging on her heels, however, resulted in a reduction in her acuity during the movement to 20/200 or less and the print appeared to oscillate up and down. Passive lateral movements of the head also resulted in a reduction in acuity to 20/200 or less but this was described as a blur and surprisingly not accompanied by any illusory movement of the environment. Several control observers showed no deterioration of vision with similar jogging on the heels or passive movements of the head.

As the patient's head was oscillated between the examiner's hands it was found that she was unable to hold fixation on the examiner as could normal subjects. Indeed, with relatively rapid oscillations of the head, the eyes moved with the head as though fixed in the orbits whereas normal subjects could hold their eyes fixed on an object despite comparable oscillations of the head.

Analogous observations were made on after-images induced with a flash of light from a discharge tube. Whereas, the after-image remained stationary for several control observers despite vigorous jogging on their heels or passive oscillations of their head, the patient observed that the after image made wide excursions up and down during the movement of her head. This, however, occurred only so long as there was light in the room to illuminate the background. In the dark or when the eyes were closed the after image did not appear to move. The after image (or the background?) moved in a vertical direction with up and down

movements of the head and in a horizontal direction with lateral movements of the head.

Rotation in a Bárány chair induced some movement of the environment, although less than normal, but no postrotary oscillopsia.

The patient's symptoms were typical of those which have been reported following streptomycin intoxication[4, 5] or loss of labyrinthine function from other causes.[6] The continued blurring of vision—not always recognized as illusory movement—with vertical movement of the head is particularly noteworthy. This was relieved by immobilization of the head. It has continued with little improvement in the subsequent five months of observation. It may be demonstrated with a measure of objectivity by testing visual acuity during vertical movement of the head or by observing an after-image during vertical movements. The blurring or illusory movement of the environment with horizontal movements was less conspicuous, but with passive horizontal movements of the head the patient was unable to maintain fixation as well as normally.

CASE 2

J. C. (Dr. Crawford) was a 30-year-old physician who received a total of approximately 275 gm. of streptomycin over a two and one-half-month period for a presumed tuberculous arthritis. A description of the patient's early symptoms and reactions has been presented in a superb autobiographical vignette published elsewhere.[7] Initially there was considerable vertigo and nausea evoked by movement of the head. Walking resulted in an apparently up and down oscillation of the environment likened to a "yo-yo." Any movement of the body and head resulted in a marked reduction in vision so that the patient was unable to recognize people while he was walking or riding in a car. The joggle of a bicycle was particularly devastating to vision. Reading on the train was impossible. Indeed, the slight movements of the head from arterial pulsation bothered his reading at first so much that it was necessary for him to hold his head still with his hands or to support it against some rigid object. All of these visual symptoms disappeared immediately as soon as he was stationary.

With appropriate tests the patient was found to have complete loss of labyrinthine function. During the subsequent period he observed illusory movement of the environment whenever he moved his head but after the initial period no vertigo occurred with movement so long as his eyes were closed. He found the disorientation was somewhat lessened as he learned to immobilize his head and to maintain his gaze on a distant object; holding onto a firm object also helped. Rapid bodily movements were accompanied by less visual disturbance than slow movements.

Examination of the patient five years after the loss of labyrinths showed no evident vestibular function with the conventional Bárány test. Superficial testing of eye movements showed nothing abnormal. There was a full range of movement in all directions without nystagmus. The following movements were executed smoothly and the opticokinetic response was symmetric. There was a suggestion of ocular motor dysmetria but this was slight and inconstant.

Visual acuity was 20/15 but jogging on the heels resulted in a reduction of the acuity during the movement to 20/70. Similar passive oscillations of the head resulted in a reduction in acuity proportionate to the violence of the oscillations. These movements were accompanied by illusory movement of the environment and it was the patient's observation that the movement per se caused the blur. Illusory movement of the environment occurred equally in the horizontal or vertical plane according to the direction of the head movements.

The patient was unable to maintain his gaze on a near object during rapid turning of his head to the right and left, as can a normal person. As in the previous patient, the eyes tended to remain fixed in the orbit when the turning became sufficiently rapid.

An after-image, induced by a flash of light, appeared to move with passive movements of the head or with jogging on the heels. This was true for both the horizontal and vertical direction but occurred only when there was at least some illumination of the room. When the room was completely dark or when the patient's eyes were closed the after-image did not appear to move. Under similar conditions the normal subject observed no movement of the after-image either in a lighted or darkened room.

This patient's early symptoms were also typical of those described with streptomycin intoxication.* As in the previous case, however, the prominent residual feature was blurring of vision with movements of the head and the blurring was evident with extraordinarily slight movements. It was demonstrable by the reduction in visual acuity

* Two other patients with streptomycin intoxication are not included in this paper for lack of more adequate work up. They did, however, complain of incapacitating and persistent illusory movement of the environment with movement of the head. The one patient on whom visual acuity measurements were made showed a deterioration of vision from 20/20 to 20/70 with mild jogging on her heels.

or by the oscillations of an after-image during movement and had persisted for at least five years after the onset of the labyrinthine disease. It is presumably permanent.

CASE 3

D. G. C. The following is a brief report of my own "labyrinthitis." Without prior warning or apparent etiology, I awoke to find that the room showed a continuous clockwise rotation whenever I opened my eyes. This was shortly followed by moderate vertigo, retching, tenesmus, and profound unsteadiness of gait. The gastrointestinal symptoms promptly abated but the spontaneous rotation of the environment continued with gradual improvement for three days. It was worse on gaze to the right or on lying on my left side. It was of course accompanied by, or caused by, a horizontal rotary nystagmus which had a fast component to the right.

The noteworthy feature of the nystagmus was that the environment always moved in one direction. This was to the right, repetitive, and synchronous with the slow component of the nystagmus. I was never aware of a movement to the left. Yet—and this seemed to me most surprising as I subsequently thought about it—there was no psychologic conflict in the fact that the environment should be back at the starting place again. In other words, I had the seemingly paradoxical experience of seeing the environment continually moving in one direction over a defined arc and yet never being aware of how it got back to the beginning of the arc nor of being bothered particularly by the inherent contradiction in this state of affairs.

One further symptom which was apparent to me but rarely mentioned so far as I am aware, was the association of a blink, or tendency to blink at the end of the slow excursion, that is, concomitant with the onset of the fast phase of the nystagmus.

As the nystagmus subsided in three days' time, and with it the vertigo, a new train of symptoms occurred characterized by illusory movement of the environment when the head was moved. This was in every way similar to that noted in the foregoing two cases. It was much more evident for horizontal than for vertical movements. There was also a definite lateralizing component for it was much more conspicuous on turning or tilting the head from right to left than from left to right. This illusory movement of the environment resulted in an annoying blur such that I was unable to recognize objects while walking or during movement. It was not always apparent that the blur was in fact due to the illusory movement. The effect might well be called simple dizziness by one not interested in analyzing it. It was accompanied by marked unsteadiness of gait and general (and spurious) sensation of inebriation. The unsteadiness of gait was not caused by the visual phenomena for it was present even with the eyes closed or in the dark. All these symptoms gradually subsided in the subsequent few weeks, but the left labyrinth gave no caloric response when tested five weeks after the onset of symptoms and six months later it was still markedly hypoactive. There was no deafness at any time.

As a symptom of unilateral labyrinthitis, illusory movement of the environment was noted to occur with the slow phase of the nystagmus, and in the opposite direction. Curiously, it did not seem unnatural that the environment should be back at the starting point during each cycle without giving evidence of how it got back there. Of incidental interest was the blink, or tendency to blink, of the lids synchronous with the fast phase of the nystagmus. Finally, the symptoms ensuing on the acute phase were similar to those described by persons who have lost their labyrinthine function through streptomycin intoxication except in the present case there was evidence of lateralization and the symptoms were temporary only.

DISCUSSION AND CONCLUSIONS

The inference is inescapable that the stabilizing effect of the labyrinths on the eyes is extraordinarily sensitive under normal conditions. It has of course been long known that the labyrinths exert positional effects on the eyes and may have well-nigh exclusive control of ocular motor function in such lower animals as the rabbit. But in man the labyrinthine control appears to play a role subordinate to that of voluntary and reflex mechanisms.[8] From the present observations, however, on patients and from threshold measurements on normal subjects,[9] it would appear that the labyrinthogenic stabilization of the eyes was of vital importance for visual function in human beings during even slight movements of the head.

The surprising feature is not the fact that the labyrinths exert an effect but rather the sensitivity of the mechanism and the magnitude of the visual deficit when the labyrinthine control is lost. Thus in both the foregoing patients who lost their labyrinths from streptomycin, jogging on the heels caused a reduction in visual acuity to

20/70 or less. The act of walking, riding in a car, or riding a bicycle so impaired vision that the patients were unable to recognize people on the street. Even the oscillations of the head from arterial pulsation so affected one of the patients that he was unable to read unless he manually supported his head. It must be inferred, therefore, that under normal conditions the semicircular canals exert a significant stabilization for even these slight head movements.

One of the curious features in these two patients was the predilection of the illusory movement of the environment for the vertical direction. Oscillations of the head horizontally induced an incapacitating blur but this was not necessarily interpreted as a movement of the environment.

Somewhat similar visual phenomena were observed in the recovery stage of labyrinthitis as described in the third case. In addition it was noted during the early events of the labyrinthitis that the nystagmus resulted in an illusory movement of the environment in one direction only (opposite the slow phase) without revealing how the environment returned to the starting point. It is curious that this paradox did not seem unnatural at the time. A further and minor feature was the blink of the lids, or tendency to blink, that was synchronous with the fast phase. These correlatives of a labyrinthine deficit do not appear to be generally appreciated, but may well be part of that vague dizziness of which patients with acute labyrinthine disturbance complain.

Summary

The visual phenomena are described in the cases of two patients who lost their labyrinthine function from streptomycin intoxication and in the case of one patient (the author) with so-called labyrinthitis. It is concluded that the semicircular canals have surprisingly important functions in stabilizing the eyes even with slight movements of the head.

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RETINAL ISCHEMIA WITH VISUAL LOSS*

Report of five cases

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Visual loss as a result of retinal ischemia is a relatively rare event in view of the frequency with which profuse bleeding occurs. It has been recognized as a type of amblyopia since antiquity, however. According to Terson,[1] Hippocrates described it as follows: "After vomiting blackish, sometimes bloody matter, the patient complains of headache and the eyes do not see." The condition has been reported following visceral bleeding, hemorrhages from wounds, and surgical procedures in which there has been extensive blood loss. It can also occur after collapse of the circulation. Of the five cases reported here, three followed prolonged bleeding, one was the result of circulatory collapse during surgery, and one followed suffocation anoxia.

The most common cause of this type of visual loss is visceral bleeding, usually from the stomach, bowel, or uterus. According to Grout,[2] 70 percent of all cases are the result of bleeding from the gastro-intestinal tract or uterus. The condition has also followed childbirth and miscarriage (Foster Moore[3]), nasal bleeding (Long[4]), urethral bleeding (Wolff[5]), and prolonged bleeding from dental extraction (Harbridge[6]). Davenport and Budden[7] reported the interesting case of a 51-year-old man who was bitten by a viper. In spite of all treatment there was bleeding from the wound and mucous membranes of the mouth, with extensive extravasation of blood into the muscles of the thigh and buttocks at the site of the penicillin injections and the application of the tourniquet. This persisted for six days when the patient began to lose vision, first in the right eye and two days later in the left.

Wolff[8] called attention to the fact that "in the olden days" one of the commonest causes of retinal ischemia with visual loss was repeated venesection. In this connection it is of interest that recurrent hemorrhaging is particularly likely to affect the vision adversely; Duke-Elder[9] states that several small hemorrhages are more likely to do so than a single large one although the amount of blood lost may be the same or less.

The resulting blindness is usually bilateral but an average of about 15 percent of all reported cases have been unilateral. Chevallereau,[9] for example, found monocular involvement in eight, or 28.5 percent, of a group of 28 cases that followed uterine hemorrhage, while in Fries' series[10] one eye was affected in only 10 percent. In discussing Wolff's paper,[5] Foster Moore suggests that unilaterality reflects a greater tendency to vascular spasm on one side of the body than on the other, as is apparent in migraine. Hogan[11] feels that unilaterality probably depends upon anatomic variations in the blood supply, that is, in a difference in the ability of the blood vessels to respond to emergencies

It is interesting that when both eyes are affected there is often an interval of several days between the dates of onset in the two eyes. In a case of Foster Moore's,[12] for example, one eye was involved 15 hours after the hemorrhage and the other eye not until three days later.

The amblyopia usually develops between the third and seventh days after the bleeding but may be delayed for a much longer time. In a review of 250 published cases, Terson[1] found that visual loss occurred during the hemorrhage in 8.3 percent, immediately after the hemorrhage in 11.6 percent, within 12 hours in 14.2 percent, within

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two days in 19.2 percent, between three and 16 days in 39.2 percent, and later than 16 days in 7.5 percent. Duggan[13] reported that visual loss could occur up to three weeks after hemorrhage but that in most cases it appeared during the first week. Fries[10] found visual loss immediate in 25 percent of cases and delayed for periods of 18 days or longer in 23 percent.

Visual loss after hemorrhage from wounds has also been reported but must be very rare indeed. Grout[2] makes the statement that during the Franco-Prussian War not a single case of visual disturbance could be attributed to traumatic hemorrhage alone. In discussing Wolff's paper,[5] Goulden stated that among all the men he saw in France during World War I who had repeated secondary hemorrhages, and were thereby reduced to severe anemia, none complained of loss of sight; he had seen records of two cases, however. Terrien[14] saw one case following a crush-injury of one leg; the visual loss was sustained 12 to 15 days after the injury. Harrington[15] also saw one case that followed a severe shrapnel wound of the thigh from which the hemorrhage was almost fatal.

Another rare cause of the condition is prolonged bleeding following surgery. In a case reported by Grossman and Holm,[16] the patient bled severely on the day thyroidectomy was performed; the operative wound had to be opened and the bleeding vessels ligated. Four days later there was sudden loss of vision in both eyes associated with the usual anemia and ischemia. Walker and Murphy[17] reported two similar cases of unilateral blindness which occurred during pulmonary excision surgery in which the prone position was used.

Retinal ischemia is also seen in states of general collapse (Duke-Elder[8]). Complete blindness, accompanied by a fixed dilated pupil, may last for days or weeks or until death has supervened. If the patient survives, optic atrophy may develop. The first of the five cases described in this report was a case of this kind. According to Rucker,[18] with whom it was discussed, the transient blindness and subsequent annular scotoma were attributable to the collapse of the circulatory system. Shock or circulatory collapse from any cause, even from treatment of hypertension by hypotensive medication, may lead to ischemia of the brain and retina. Rucker felt that the ophthalmoscopic picture in Case 1, which resembled that presented by closure of the central retinal artery, was reasonably typical. The retina may be affected earlier than the brain, or may be affected without the brain's becoming involved, as happens to aviators when they dive for bombing and black out before they lose consciousness. In Rucker's opinion the picture resembles that induced by repeated massive hemorrhage.

Lebane[19] reported a case of transient blindness following blood transfusion. A 42-year-old man had stomach bleeding followed by marked anemia, the blood picture showing 2,700,000 red cells and a hemoglobin of 50 percent. He was given a transfusion with a view to improving his condition preparatory to laparotomy. Fifteen minutes after the completion of the transfusion he had a mild reaction which lasted 10 minutes and was followed by sleep. Upon waking an hour later he was blind. The fundus examination showed no evidence of arteriospasm or hemorrhage. There was a gradual return of vision over a period of an hour and a half. The cause of the visual loss was never determined. In a similar case Walsh[20] reported spasm of the retinal arteries with complete blindness in one eye a few days after transfusion, with involvement of the other eye several days later. Since transfusions are often given to patients suffering from blood disease or anemia, one wonders whether the transfusion is a trigger mechanism for the production of arteriospasm, or entirely incidental.

Clinical picture

Ulrich[21] examined the fundi of a patient 10 minutes after he had become unconscious from extensive recurrent stomach hemor-

rhage. He found the disc pale and the arteries contracted, partly filled, and difficult to follow to the disc. The veins were somewhat dilated, and near the disc they were bright red in color as if they had been transformed into arteries. Near the disc were numerous retinal hemorrhages. The macula was distinct and dark in color; surrounding the fovea were cracked varnishlike white streaks, similar to those seen in the retinitis of albuminuria. The vision was reduced to counting fingers. Similar findings were recorded by Hoffman.[22]

According to Duke-Elder,[23] the typical clinical picture consists of a dilated and fixed pupil, a pale disc, and marked spasm of the retinal arteries with edema, sometimes generalized over the posterior pole, and sometimes in fluffy patches associated with scattered retinal hemorrhages that suggest the changes of renal retinopathy. In some instances the fundus may look quite normal, and in others the entire retina may be edematous with a cherry-red spot at the macula such as is seen in complete obstruction of the arterial circulation. Wolff[5] found great variety in the fundus picture but stated that in a typical case the arteries were very fine and the disc pale.

After the acute process has subsided, the fundi often reveal numerous pigment deposits throughout the periphery, marked deposition of pigment in the area of the macula, and finally some degree of optic atrophy. In the worst cases atrophy may be complete.

Visual prognosis

Although it is certain that permanent blindness results in a large percentage of cases (30 to 50 percent, according to Duke-Elder[8]), statements on prognosis must be guarded. On the one hand there is the extreme view of Foster Moore[3] that complete recovery never occurs, and on the other there is Ulrich's case[21] in which in two months' time the vision returned from counting fingers to 20/20 in each eye and the fundi recovered their normal appearance. Terson[1] found that only 50 percent showed improvement in vision but that 10 or 12 percent of these recovered normal vision. The prognostic problem is complicated by the fact that some patients who seem to be mildly affected do not recover their visual loss, while others who have been totally blind may show a remarkable degree of recovery. The improvement may not be the same in both eyes, moreover. In Sweet's patient,[24] for example, the field improved and the vision returned to 20/20 in the right eye while the left eye remained blind.

Visual field changes

According to Harrington,[15] there are two principal types of visual field defect which follow severe hemorrhage. These are (1) extreme contraction and (2) altitudinal hemianopsia. There is considerable variation in the degree of field depression, and the fields in the two eyes are usually not symmetrically affected. The central vision may be spared or obliterated. When the upper or lower half of the field is lost there is often a small area of macula that is spared.

In a study of the literature, Grout[2] found the lower half of the field lost in 23 percent, concentric contraction in 20 percent, a central scotoma in 13 percent, and homonymous hemianopsia in 10 percent. Loss of the lower half of the field is thus the commonest field defect; that is, if any part of the field is retained, it is usually the upper field. As stated above, the involvement may not be the same in the two eyes. Davenport and Budden's patient[7] lost the entire lower field in the right eye but retained 20/20 vision; in the left eye there was minimal light perception, more definite in the upper field. Loss of the upper field is very rare; Grout[2] found it noted in the records of a single eye only.

Duggan[13] feels that when there is a central scotoma with a normal fundus, the lesion may be retrobulbar in character but that the basic pathologic process is probably the same as it is in cases of central retinal artery closure.

In the group of cases with homonymous hemianopsia, Amos's case[25] is particularly interesting. Uterine hemorrhage was followed by right homonymous hemianopsia, and a second uterine hemorrhage some time later was followed by left homonymous hemianopsia, with the preservation finally of only a minute central field. The homonymous hemianopic field changes suggest that the visual loss is cortical in nature, probably a result of cerebral anemia.

In rare instances there is a significant return of the visual fields after recovery from the hemorrhage.

Etiology

There has been considerable discussion of the cause of the acute retinal ischemia in these cases. Many years ago Leber[26] stated that the ocular changes were produced not only by direct loss of blood but by retardation of the circulation which resulted in edema and multiple retinal hemorrhages.

Wolff[5] attributed the ischemia to spasm of the arteries due to lack of oxygen. In quinine amblyopia the arteries are greatly narrowed and the disc is pale. Since quinine inhibits the oxidizing power of the blood, oxygen is given off less freely. This, Wolff feels, substantiates the lack-of-oxygen theory and indicates that recurrent hemorrhage with reduction in hemoglobin over a period of time is the chief etiologic factor. The fact that the onset of blindness is frequently accompanied by faintness, giddiness, and even loss of consciousness (all signs of general oxygen lack), may be construed as corroborative evidence.

The rarity with which amblyopia follows traumatic hemorrhage is explained by the fact that such hemorrhage occurs in normal individuals with high hemoglobin levels and normal blood-forming organs, and that as a rule it is not recurrent. In such patients the normal hemoglobin level would be recovered more rapidly than in patients suffering, for example, from a bleeding gastric ulcer and an already reduced hemoglobin level. It is to be recalled that the amblyopia develops as a rule between the third and seventh days after the hemorrhage.

A further fact seeming to confirm the theory that spasm of the arteries is due to lack of oxygen is that in a number of cases the upper fields have remained intact after the hemorrhage, only the lower field showing a loss in vision. Pincus[27] has reported that when it is possible to take fields, the lower fields are shown to have suffered more than the upper. Wolff[5] feels that this can be explained on the basis of gravity, the lower part of the retina receiving more blood than the upper and thus being less susceptible to spasm. As mentioned above, Foster Moore[3] suggested that the unilaterality observable in some cases is a reflection, as in migraine, of a more marked tendency to vascular spasm on one side of the body than on the other.

Harrington[18] has expressed the view that permanent visual loss is probably due to hypoxia in the ganglion-cell layer of the retina. Duggan[13] feels that the toxin responsible for the amblyopia is a vasoconstrictor, probably epinephrine, and that its increased output is due to homeostatic reactions to the hemorrhage. Duke-Elder[28] states that the amblyopia is probably not due to ischemia alone but may perhaps be associated with a hemoclastic shock or anaphylactic crisis, or to a toxemia due to extensive hemolysis or the liberation of epinephrine-like substances. Rucker[18] is also convinced that the visible changes and consequent loss of vision are not due to the ischemia alone but that there is some additional factor not understood at the present time, perhaps resembling shock or anaphylaxis or toxemia.

Pathology

The rarity of this condition has severely limited the study of its pathology. Such observations as have been made, however, indicate that in the early stages there is papillary stasis, with general retinal edema and degeneration of the ganglion cells and nerve

fibers and without any evidence of inflammation. Later there is complete optic atrophy which Ziegler,[28] as long ago as 1887, felt was the result of ischemia rather than of retrobulbar neuritis. His findings and those of other early investigators were confirmed in 1922 by Uhthoff.[29]

In 1899 Holden[30] made a particularly interesting study of the retinal changes in dogs bled experimentally. Fifteen days after the last bleeding the retinas exhibited signs of edema of the nerve-fiber and ganglion-cell layers, and a lack of granules in the nuclei of the inner nuclear layer. The ganglion cells were in a more advanced stage of degeneration and more cells were involved than in animals killed 24 hours after the bleeding. The pathologic condition, then, was a degeneration of a number of retinal ganglion cells, together with their long processes which make up the centripetal fibers of the optic nerve. This explains the typical case in which vision fails in the entire field or a portion of the field, but is inadequate to explain the rare case in which the visual disturbance assumes the form of a central scotoma and the ophthalmoscopic changes indicate retrobulbar neuritis. As already noted, Duggan[13] feels that the basic pathology of the retrobulbar neuritis cases is the same as the pathology of central retinal artery closure.

Treatment

According to Duke-Elder,[23] the value of treatment, even if applied early, is equivocal. It should be directed first of all to combatting systemically the effects of the loss of blood; that is, the hemorrhage must be stopped and the circulation maintained by transfusions of saline or, better, of blood. Local measures also should be directed toward maintaining the circulation.

In 1883 Hoffman[22] advocated the use of strychnine injections, and in 1934 Hartmann and Parfonry[21] reported improvement in vision from total blindness to 20/40 in each eye after the use of acetylcholine. Duggan[13] has also been a strong advocate of vasodilators, but in the hands of most observers their use has been very disappointing. Grossman and Holm[16] tried vasodilators without success for three days and then, on the 10th day after hemorrhage, gave the patient a bilateral stellate ganglion block. There was improvement in vision within 10 minutes. In order to maintain the vasodilation they also administered 1,000 cc. of 0.1-percent procaine intravenously by the drop method.

Duke-Elder[23] reported that blood transfusions combined with ocular paracentesis had also been tried in an effort to induce local vasodilation, but without striking results. Fuchs[32] reported a case of blindness following severe postpartem hemorrhage. A transfusion of 250 cc. of blood was given at once and the patient reported improvement before it was concluded. A second transfusion was given four days later. Six weeks later the patient had normal vision with slight narrowing of the arteries and a slight contraction of the superior field of vision. Frey[33] believes that repeated transfusions are valuable in preventing retinal anoxemia by maintaining the blood volume and normal pressure.

Case reports

Case 1

S. B., a 19-year-old girl, was seen on May 19, 1954. She had been referred from another city because of loss of vision in the left eye following surgery. On February 22, 1954, she had had a Cesarean section. During surgery she had a circulatory system collapse and was resuscitated with difficulty. Within 24 hours she complained that she could not see with the left eye. The results of ophthalmologic examination made at that time by Dr. Grant Balding of Pasadena, California, were as follows:

External examination. Negative.

Fundus examination. R.E., normal; L.E., the media were clear. The disc was obscured by edema which extended over the fundus with a cherry-red spot in the macula. The picture resembled that produced by an occlusion of the central retinal artery.

Treatment. Priscoline, Diamox, and thiamin were ordered and the patient returned home in two weeks.

On May 19, 1954, the findings were:

Vision. R.E., 20/20; L.E., 20/200+1, unimproved by lenses.

External examination. Negative.

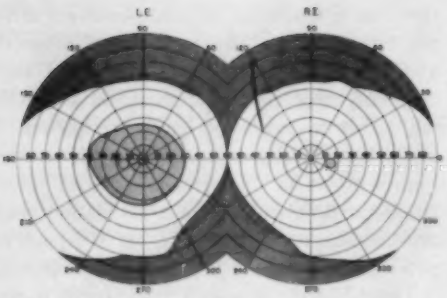

Fig. 1 (Cordes). S. B., March 19, 1954. 3/300. Ring scotoma left eye. Vision: R.E., 20/20; L.E., 20/200.

Fundus examination. R.E., normal; L.E., the media were clear. The disc was partly atrophic with some blurring of the disc margins and some connective tissue on the disc. Over the posterior pole there was marked disturbance of the pigment with fine clumping both in the deep layers and in some areas covering the vessels. The macula seemed to be involved in about the same degree as the rest of the posterior pole.

Visual fields. R.E., normal; L.E., there was an island of vision within two degrees of fixation, surrounded by an annular scotoma of from 30 to 40 degrees (fig. 1).

Treatment. Vasodilators were prescribed.

Result. There was gradual improvement until at the time of the last examination on October 17, 1954, the vision in the left eye was 20/20—2, and the field showed an annular scotoma of approximately 20 degrees surrounding a central area of five degrees (fig. 2).

CASE 2

A. F., a 48-year-old woman, was seen by her internist on April 15, 1955. She complained that four months previously she had developed increasingly severe back pain and headache for which she had taken a good deal of aspirin. At this time she consulted her home town physician and

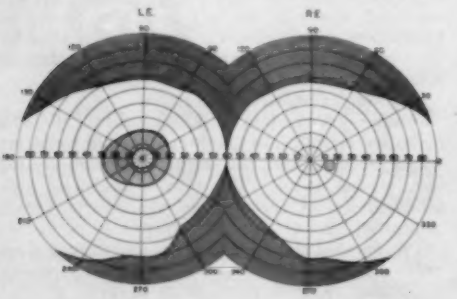

Fig. 2 (Cordes). S. B., August 17, 1954. 3/300. Scotoma left eye reduced in size. Vision: L.E., 20/20.

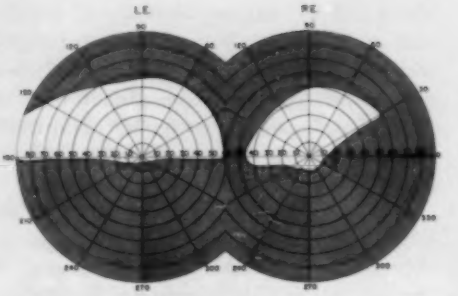

Fig. 3 (Cordes). G. E., April 28, 1955. 3/300. Showing loss of lower field in both eyes. Vision: R.E., 20/30; L.E., 20/30+.

reported to him that for two days prior to seeing him she had noted gross blood in her stools but had not had lower abdominal cramps. She was told to return after her next period and was given sodium bicarbonate and milk of magnesia.

Upon returning home she took this medication and at once began to vomit large quantities of dark red blood and to have grossly bloody stools. These symptoms continued for three days at home while she became weaker and weaker. Her physician was called and immediately sent her to the hospital where she was given transfusions. Between 12 and 16 hours later she went into shock for a period of one hour. Upon reviving she was totally blind. Over the course of the next two days and following further transfusions, her sight returned but there was a residual inferior hemianopsia. Her blood count when she entered the hospital showed "marked anemia."

Physical examination failed to reveal any pathologic alteration in the gastro-intestinal tract and her internist felt that the excessive, prolonged use of aspirin may have been responsible for the bleeding.

Following her stay in the hospital her husband noted that she was slower in concentrating and responding to questions. It was felt that this could have been due to cerebral anemia.

On April 28, 1955, seven weeks after the initial loss of vision, an ophthalmologic examination revealed the following:

Vision. R.E., 20/30 (with correction); L.E., 20/30+ (with correction).

External examination. Negative.

Fundus examination. There was a definite atrophy of the upper halves of the discs in both eyes, and the arteries over the upper portions of the fundi showed definite contraction in contrast to the arteries over the lower halves.

Visual fields. There was loss of the lower fields in both eyes, with some additional loss above the horizontal midline in the upper temporal quadrant of the right eye. The macula was spared in both eyes (fig. 3).

Treatment. Vasodilators were prescribed for a

period of six months and the patient was observed periodically.

Result. When last measured on June 27, 1957, the vision was 20/20—3 in each eye. The visual fields remained the same as at the initial examination.

CASE 3

G. B., a 33-year-old woman, was seen on March 4, 1946. She complained of vaginal bleeding of 10 days' duration, and of blurred vision in the left eye for one day.

The patient's menarche was at the age of 12 years. The periods had been irregular and at times prolonged. She had had periods of amenorrhea on the one hand and of continuous vaginal flow on the other for periods as long as a year. From September to early December, 1945, she had had bleeding nearly every day, increasing in amount. Her blood count at that time was 4,500,000 red cells and her hemoglobin level 79.8 percent.

On February 23, 1946, she began what she regarded as a normal menstrual period. It lasted five days. On March 1st, she had a sudden profuse vaginal hemorrhage which her physician checked in two days. Late in the afternoon of March 3rd she developed a rather severe headache and again began to flow heavily. She noticed that the vision of the left eye was blurred, especially when she looked directly at an object.

When admitted to the hospital at this time the patient was weak and acutely ill. Her temperature was 100.8F., her pulse was 100, her respirations were 20, and her blood pressure was 135/70. Her hemoglobin was 10.6 gm., and her red blood cell count was 3,640,000.

On March 4, 1946, an ophthalmologic examination revealed:

Vision. R.E., appeared normal; L.E., counting fingers.

External examination. Negative.

Fundus examination. R.E., normal; L.E., the media were clear. The disc margins were indistinct, especially temporally, inferiorly, and nasally, and there was a measurable papilledema of from two to three diopters. The physiologic cup was completely filled. Inferiorly the edema of the disc extended into the retina for some distance. One-half disc diameter from the disc was an elevated, gray-white area of edema. Beyond this the retina showed a number of fine linear hemorrhages and a few well-defined exudates. The retinal veins in this area appeared to be dilated. The arteries were partially covered by edema and it was difficult to determine their caliber. They did not appear to be attenuated, however.

Visual fields. Could not be measured at this time.

Course. During her stay in the hospital the patient's vision improved slightly and the edema of the disc and the retinal lessions improved considerably. Following transfusions and medical treatment she left the hospital on March 18, 1946, with her general condition improved.

This patient was not seen again until October, 1946 (seven months later), when she was examined in the hospital before complete hysterectomy for carcinoma of the uterus. The vision of the left eye was still markedly impaired. Because of her acute illness it was impossible to measure her visual fields. As a result of her failure to keep office appointments, the visual fields of this patient were in fact never determined. She died of metastases on April 29, 1949.

CASE 4

F. R., a 49-year-old woman, entered Moffit Hospital on August 4, 1957, with a diagnosis of bleeding duodenal ulcer. The hemoglobin level was 26 percent. This was elevated to 41 percent by transfusions of blood. Subsequently the patient vomited a considerable amount of blood and the hemoglobin dropped to 32 percent.

An emergency subtotal gastrectomy and gastrojejunostomy was performed on August 9th. The postoperative course appeared to be normal until the following day when the patient told the nurse that her vision was very poor and that she could see nothing but "fuzzy objects." This was accompanied by an increase in blood pressure to hypertensive levels and by albuminuria.

Ophthalmologic examination revealed:

Vision. R.E., counting fingers at five feet; L.E., counting fingers at six feet.

External examination. Negative.

Fundus examination. Both discs were normal. The arterioles exhibited marked localized and generalized spasm with a tendency to dilate and collapse readily under direct observation. There were no visible hemorrhages or exudates.

Course. During the next two days there was gradual improvement in vision with return to normal. When it was possible to measure the visual fields they were found to be normal.

CASE 5

P. E. T., a 21-year-old man, was admitted to Moffit Hospital on August 4, 1957. Five days before entry he had been accidentally buried in sand for an unknown length of time. After his rescue he was unconscious for 44 hours. During this time he underwent decerebrate rigidity but his condition improved after he regained consciousness. Two days before admission to the hospital, that is, three days after his accident, his vision began to dim bilaterally, and on the day of admission he claimed total blindness.

The general physical examination was unremarkable except for subcutaneous emphysema over the entire surface of the abdomen and down the flanks. Examination also revealed marked incoordination in the finger-to-nose and heel-to-shin tests.

Ophthalmologic examination revealed:

Vision. R.E., counting fingers at eight feet; L.E., counting fingers at six feet.

External examination. Negative except for some

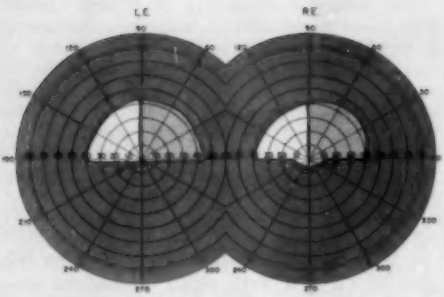

Fig. 4 (Cordes). P. E. T., August 16, 1957. Complete inferior altitudinal hemianopsia with macular region appearing to be split. Vision: R.E., counting fingers at five feet; L.E., counting fingers at six feet. White area: 5/330. Stippled area: 10/330.

difficulty on lateral rotation of the eyes to the right.

Fundus examination. The discs were flat but somewhat pale. The retinal arterioles were definitely narrowed and the arteriovenous ratio was abnormal. There were no exudates or hemorrhages.

Visual fields. There was complete inferior altitudinal hemianopsia which seemed to begin at the horizontal midline or slightly above. The macular region appeared to be split during this field examination (fig. 4).

Treatment. Nicotinic acid, 100 mg., was given every six hours, and seven liters of a carbon dioxide (10 percent)-oxygen (90 percent) mixture were given during a 10-minute period every hour. On August 11th a bilateral cervical stellate block was established with one-percent novocaine.

Result. On August 16th the fields had improved and the visual acuity had returned to 20/30 in each eye. While the fields still showed an inferior altitudinal hemianopsia, it was much less dense and the patient could see a 50-mm. target in the lower fields. With a five-mm. target at 330 mm. there was a homonymous defect involving the right upper quadrant. The best field was the upper left (fig. 5). The patient was last seen November 20, 1957, the vision now being 20/20 in each eye and the fields continuing to improve.

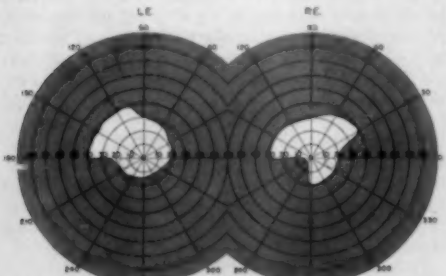

Fig. 5 (Cordes). P. E. T., September 16, 1957. 5/1000. Vision: R.E., 20/30; L.E., 20/30.

Comments

Case report 1. The retinal ischemia in this case followed collapse of the circulatory system. As has often been reported in these cases, the initial picture observed within the first 24 hours suggested an occlusion of the central retinal artery. It is of interest that there was a central scotoma with sparing of the macula. In view of the fundus picture at the time of visual loss and the permanent retinal pigment changes, this cannot be regarded as belonging to the group of scotoma in which the pathology is believed to be retrobulbar. It is also noteworthy that this case was one of the minority in which there is improvement in vision but, as is usually the case, recovery was incomplete. It was also one of the small proportion (15 percent) that are unilateral. In view of the experience reported in the literature, it is difficult to say what, if any, effect the vasodilators had on the recovery of vision.

Case report 2. The second case reported may be regarded as typical in that there was a history of repeated bleeding with the development of anemia followed by visual loss. There was a return of the upper fields of vision with a sparing of the macula in each eye so that central visual acuity returned approximately to normal. Of special interest in this case is the fact that following one transfusion the patient went into shock and upon reviving was totally blind. This corresponds with the experience of Lebane[19] whose patient developed anemia after prolonged stomach bleeding, and who was given a preoperative transfusion. An hour after the transfusion, and following a mild reaction, the patient awoke totally blind. The vision gradually returned over a period of an hour and a half.

Repeated transfusion has been advocated as treatment in these cases, but although this patient (Case 2) received a total of eight

transfusions, there was no return of the lower field of vision.

Case report 3. The development of ocular ischemia, and possibly also of cerebral ischemia, in this patient followed the commonly described pattern for lesions of this type. The patient had had several attacks of prolonged vaginal bleeding prior to the onset of the severe hemorrhage that accompanied the ocular condition. The case was another of the small group in which the involvement is monocular, and its course supports the view that treatment, transfusion in this case, is of little avail.

Case report 4. In this case of visual loss following retinal ischemia, there was no retinal edema or hemorrhage and the vision recovered completely in a short time. This can perhaps be explained by the fact that the spasm of the arteries, as directly observed, was intermittent so that there was a supply of oxygen sufficient to prevent visible changes in the retina but not sufficient to prevent visual loss. The fact that the spasm subsided soon after the onset of visual disturbance could also explain the rapid complete return of vision. The picture may have been similar to that of Lebane's case[10] of marked anemia from recurrent bleeding in which the visual loss was transient and no arterial spasm was observed. The arterial spasm may have occurred at the time of reaction and have already disappeared by the time the fundi were examined an hour later.

Case report 5. The field defects seen in this case of anoxia from suffocation resemble those found in anoxia from exsanguination. The fact that the blood and blood-producing organs were normal may explain the absence of permanent visible retinal changes. The altitudinal field defect was probably retinal in origin following retinal arteriolar spasm. The additional homonymous defect to small test objects would indicate that there was cerebral damage as well.

Of particular interest was the hemianopsia. As stated above, the literature indicates that it occurs in about 10 percent of cases. Harrington, with whom the case was discussed, feels that the cause of the hemianopsia can be presumed to be the result of an associated cerebral anoxia in addition to the retinal anoxia. This also coincides with Rucker's opinion that in these cases there may or may not be involvement of the brain as well as the retina.

In any event, if the interpretation of this case is correct it would seem to substantiate the theory that the changes in these cases of retinal ischemia are the result primarily of anoxia.

Summary

Five cases of retinal ischemia associated with visual loss are presented. The first was associated with circulatory collapse occurring during cesarean section. In Cases 2, 3, and 4 there was the usual history of repeated prolonged bleeding from the stomach, uterus, and a duodenal ulcer, respectively.

Most observers feel that anoxia with resultant arteriospasm is the primary factor in the production of the visual loss in these cases. In Case 5 an uncomplicated anoxia resulting from accidental burial in sand produced an ocular picture typical of the type of case under discussion.

That there are factors as yet not understood seems apparent from Case 2 in which the visual loss seemed to be directly associated with recovery from transfusion shock.

In one patient there was complete recovery of vision, due perhaps to the fact that the arteriospasm, as directly observed, was intermittent and did not persist too long.

Treatment in these cases included vasodilators of various types, transfusions (Case 2 had eight), carbon dioxide-oxygen inhalations, and bilateral cervical stellate ganglion block with one-percent novocaine. In none of the patients did therapy seem to be a clear-cut factor in recovery.

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INFLUENCE OF THE EPITHELIUM ON THE HEALING OF CORNEAL INCISIONS*

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Studies of the repair of limbal and corneal incisions show that healing takes place more rapidly in the anterior than in the posterior part of the wound.[1] Moreover, it is known that the first reparative changes in stromal cells and ground substance occur beneath the epithelial plug.[2] Inasmuch as there is considerable evidence that most corneal metabolism takes place within the epithelium, one may inquire if the presence of epithelium on the anterior surface of the cornea influences the rate of stromal healing.[3,4]

Recently published investigations by one of us have established the normal increase in number of fibroblasts in the wound edges during the first 120 hours.[5,6] No fibroblasts were present in corneal incisions examined within the first 12 hours but by the 24th hour there were 35 such cells per oil immersion field. This number increased to 162 by the 60th postoperative hour. At 120 hours they were so numerous that counts could no longer be made. These studies also showed the fibroblasts arose first from stromal cells at the wound edge and later from monocytes which had migrated from the limbus. Both the corneal stromal cells and the monocytes became macrophagelike before their transformation into fibroblasts. With these findings in mind, the following experiments were conducted to determine the fibroblast content of healing corneal incisions after removal of the epithelium.

METHOD

The experimental animals were rats. After anesthetizing them with ether, standard two-mm. penetrating incisions were made in the center of the cornea. The animals were killed 24, 36, 48, 72, and 96 hours after operation, the eyes enucleated, and fixed in formalin-alcohol solution. Whole thickness strips of cornea were cut at right angles to the incision and prepared with Giemsa stain. Cell counts on these mounts were made according to the method recently described.[5]

The eyes were grouped as follows:

I. *Controls.* Two-mm. standard penetrating corneal incision.

II. *Application of one drop of cocaine* (four-percent solution) followed in five minutes by standard corneal incision.

III. *Application of one drop of cocaine* (four-percent solution) followed by five minutes by removal of epithelium with cotton swab and standard corneal incision.

IV. *Application of one drop of cocaine* (four-percent solution) followed in five minutes by removal of epithelium with subsequent daily removal of epithelium. Cocaine used only on the first day†

V. *Application of one drop of cocaine* (four-percent solution) to cornea followed in five minutes by removal of epithelium with cotton swab. No incision.

RESULTS

The cellular changes were observed both at the wound edge and throughout the cornea:

1. *Changes at the wound edge* (table 1). The fibroblast count in the control eyes was similar to that previously reported.[5] When cocaine was applied at the time of operation (Group II), the number of fibroblasts along the wound edges was only 50 percent of the normal number at the end of 24 hours. However, this decrease was transient and the count returned to normal between the 24th and 72nd hour (fig. 1B). In those eyes

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† The regeneration of corneal epithelium was determined by staining with fluorescein (two-percent solution).

TABLE 1

INFLUENCE OF THE EPITHELIUM ON THE HEALING OF CORNEAL INCISIONS

Fibroblasts per Oil Immersion Field
(At Wound Edge After Standard Incision)

Age of Wound (hrs.)	Group I Control		Group II 1 Drop Cocaine 4%		Group III Epithelium Removed Once		Group IV Epithelium Removed Daily	
	No. of Eyes	Mean No. of Fibroblasts (±S.E.*)	No. of Eyes	Mean No. of Fibroblasts (±S.E.)	No. of Eyes	Mean No. of Fibroblasts (±S.E.)	No. of Eyes	Mean No. of Fibroblasts (±S.E.)
24	5	30.0 (± 1.6)	5	18.5 (±4.0)	5	15.7 (± 4.4)		
36	5	60.3 (± 5.7)	4	40.1 (±2.6)	6	14.3 (± 4.5)	6	10.6 (± 2.0)
48	4	93.8 (± 6.2)	5	65.7 (±4.1)	6	41.4 (± 7.5)	6	7.5 (± 3.9)
72	5	208.6 (±17.5)	4	178.0 (±5.3)	4	79.9 (±12.1)	7	10.3 (± 7.5)
96	8	too thick to count	8	too thick to count	4	127.8 (± 4.5)	6	36.0 (±13.4)

* S.E. = Standard error of the mean.

in which epithelium was removed only at the time of operation (Group III) the initial decrease in fibroblasts was similar to that noted in the cocaine group, but the rate of return to normal was much slower (fig. 1C). It was not until the 48th hour that an increase in the number of fibroblasts was found (table 1). At 96 hours the cell count was still considerably below that of the control eyes. This finding is of particular interest inasmuch as fluorescein staining showed epithelium did not grow into the incision until about the 48th hour. Daily removal of epithelium (Group IV) caused a prolonged decrease in fibroblast proliferation (figs. 1D and 2D). After 96 hours the cell counts in these wounds were only equivalent to those of a normal 24-hour incision.

2. *Cellular changes in the corneal stroma distant from the wound.* In the control group

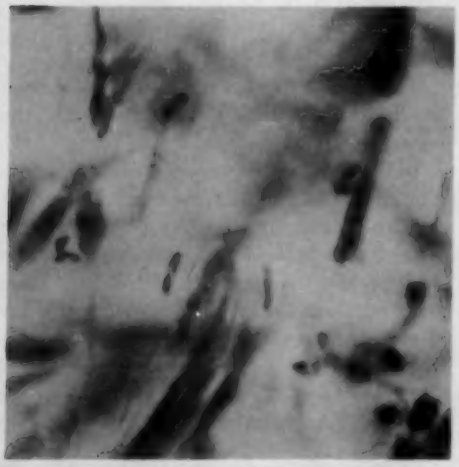

Fig. 1A (Dunnington and Weimar). Fibroblasts in a corneal wound 36 hours after operation. (Control.)

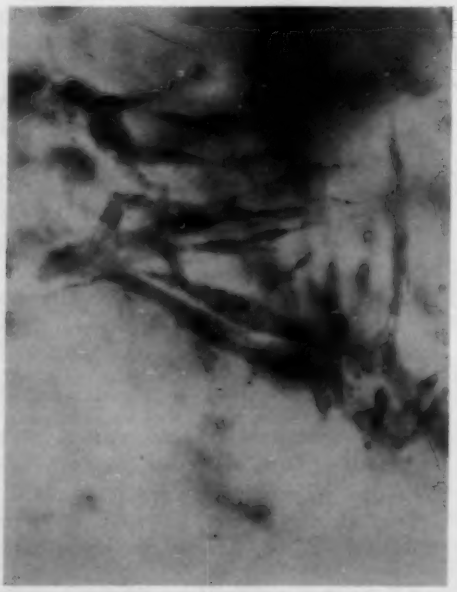

Fig. 1B (Dunnington and Weimar). Fibroblasts in a corneal wound 36 hours after operation. (Cocaine application.)

(Group I) and in the wounds treated with cocaine alone (Group II) no changes were noted in the corneal stromal cells 250 microns distant from the wound (figs. 3A and 3B). In all eyes in which epithelium had been removed (Groups III, IV, and V), the corneal stromal cells throughout the denuded area assumed fibroblastlike forms by the 24th hour. However, this was temporary for

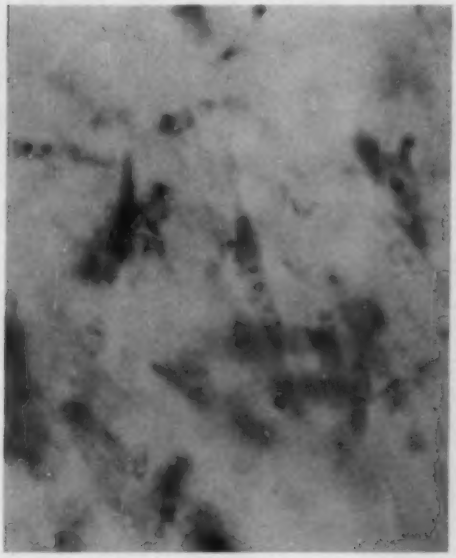

Fig. 1C (Dunnington and Weimar). Fibroblasts in a corneal wound 36 hours after operation. (Epithelium removed once.)

Fig. 2A (Dunnington and Weimar). Fibroblasts in a corneal wound 72 hours after operation. (Control.)

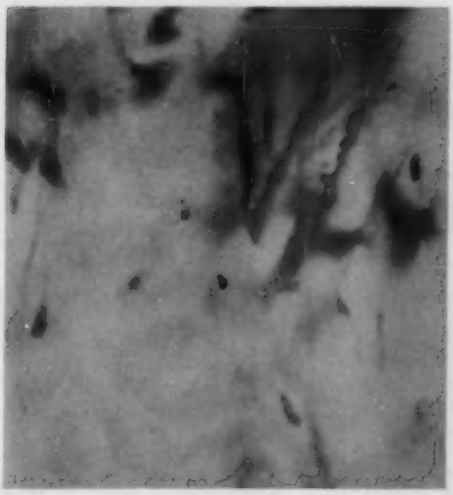

Fig. 1D (Dunnington and Weimar). Fibroblasts in a corneal wound 36 hours after operation. (Epithelium removed daily.)

Fig. 2B (Dunnington and Weimar). Fibroblasts in a corneal wound 72 hours after operation. (Cocaine application.)

by the 36th hour these cells had largely resumed their normal appearance. At the end of 48 hours, if re-epithelization had not been interrupted, the corneal stromal cells once more became fibroblastic in appearance. The cells maintained this form for the next 24 to 36 hours and then gradually resumed their normal characteristics (fig. 3C). By the 96th hour numerous monocytes had invaded the corneal stroma.

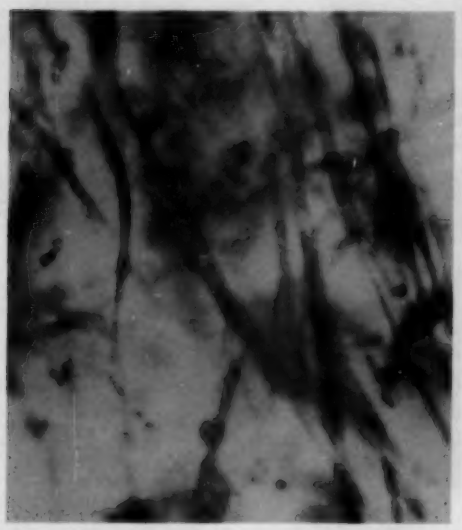

Fig. 2C (Dunnington and Weimar). Fibroblasts in a corneal wound 72 hours after operation. (Epithelium removed once.)

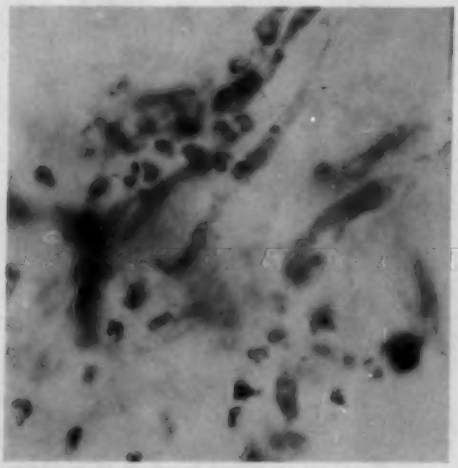

Fig. 2D (Dunnington and Weimar). Fibroblasts in a corneal wound 72 hours after operation. (Epithelium removed daily.)

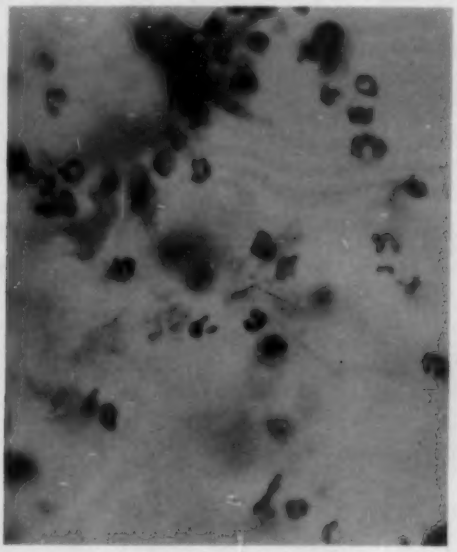

Fig. 3A (Dunnington and Weimar). Cellular changes in corneal stroma 250 microns distant from incision 72 hours after operation. (Control.)

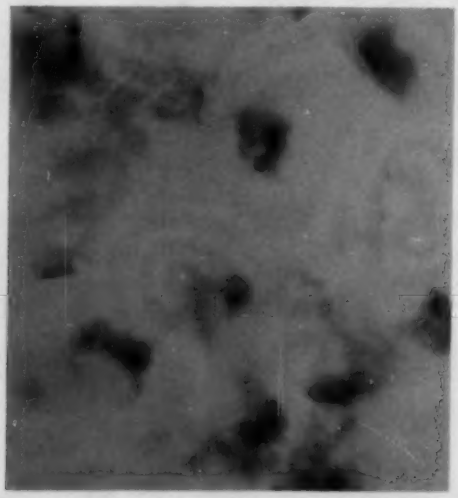

Fig. 3B (Dunnington and Weimar). Cellular changes in corneal stroma 250 microns distant from incision 72 hours after operation. (Cocaine application.)

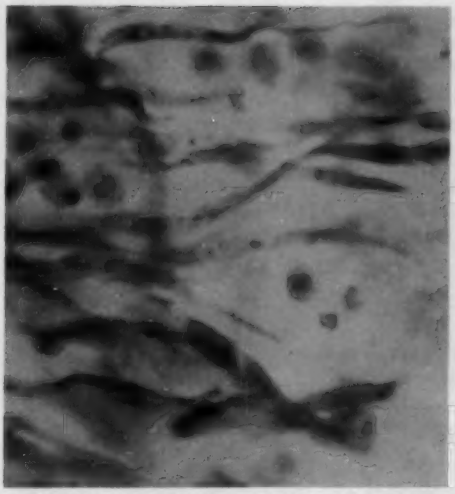

Fig. 3C (Dunnington and Weimar). Cellular changes in corneal stroma 250 microns distant from incision 72 hours after operation. (Epithelium removed once.)

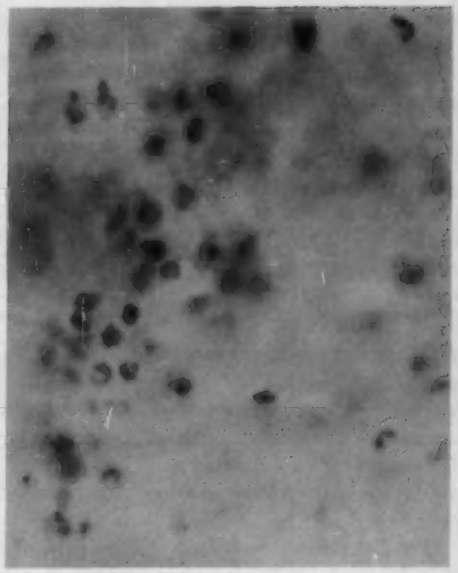

Fig. 3D (Dunnington and Weimar). Cellular changes in corneal stroma 250 microns distant from incision 72 hours after operation. (Epithelium removed daily.)

When the epithelium was removed daily (Group IV) the stromal cells assumed fibroblastlike forms at the end of 24 hours, but did not undergo a second transformation (fig. 3D). The difference in reactions in the epithelized and nonepithelized areas was strikingly shown at the limbal zone. In this region, despite efforts to remove all the cells, a ridge of epithelium frequently did develop 96 hours after operation. Beneath this regenerating epithelium there was an intense transformation of corneal stromal cells into fibroblastlike forms which was in marked contrast to lack of such activity in the nonepithelized portion. It is also interesting to note that the polymorphonuclear invasion of the stroma was approximately equal in the presence or absence of stromal cell transformation.

Discussion

There have been very few investigations of the influence of epithelium on the healing of underlying connective tissue. In 1936 Bentley reported in vitro studies of healing in embryonic rat skin after a central disc of tissue had been removed.[7] He demonstrated that reparative processes in connective tissue take place only at sites where epithelium has spread over the wounded area. The connective tissue changes observed consisted of activation and multiplication of fibroblasts, thickening and increase in intercellular fibrils, and orientation of both components to the epithelium. Bentley's results are somewhat analogous to our findings both of which indicate that the regenerating epithelial cells play an important role in activating the underlying stromal cells. The presence of fibroblasts at the wound edges at the end of 24 hours strongly suggests that epithelium is at least partly responsible for this rapid response. In view of the well-known inhibitory effect of cocaine upon the regeneration of epithelium, it is not surprising that in wounds so treated the fibroblast formation was depressed.[8] The failure of the corneal stromal cells to undergo transformation in the absence of an epithelial covering is additional evidence that important stimuli to connective-tissue formation

exist within the regenerating epithelial cells.

The nature of these stimuli is the subject of much speculation. Recent investigations have shown that within 12 hours after injury all the stromal cells in a wounded cornea become transformed into macrophagelike cells. This activity precedes their transformation at the wound edge into fibroblasts.[6] Chevremont has demonstrated in tissue culture that choline specifically induces the transformation of cells of many types (for example, muscle cells, connective tissue cells, vitelline entoblasts) into macrophages.[9] He has suggested that this choline is derived from either lecithin or acetylcholine. Since corneal epithelium is especially rich in acetylcholine it may perhaps be the source of an essential substance for transformation of stromal cells.[10, 11]

Tissue culture studies of the capacity of epithelial cells to digest plasma clots indicate their high content of proteolytic enzymes.[12] Simms[13] and Simms and Stillman[14] have found that trypsin or papain treatment enhances the growth of adult tissues in tissue culture. Furthermore, it has long been known that proteoses derived from the proteolytic digestion of proteins facilitate the growth and division of fibroblasts. In tissue culture the presence of such proteoses causes monocytes to assume the morphologic appearance of fibroblasts. The absence of such compounds leads fibroblasts to assume the morphologic appearance of monocytes.[15, 16]

In animals under prolonged anesthesia the transformation of corneal stromal cells to fibroblasts is inhibited. This phenomenon can be overcome by the topical application of trypsin.[17]

The role of the epithelial metabolism in the induction and maintenance of these transformations is unknown. However, biochemical studies indicate that the oxidative metabolism of the cornea takes place chiefly in the epithelium.[4] There is also histochemical evidence that the dehydrogenases and cytochrome oxidase are located in the epithelium.[18, 19] Since oxidative pathways are the chief source of the high energy yielding reactions necessary to growth, it seems possible that the metabolism of the epithelium promotes the more rapid healing found in the anterior part of the corneal wound.

Summary

Experimental studies show that the epithelium exerts a profound effect upon fibroblast formation in a healing corneal wound. In its absence fibroblast formation is decreased and does not reach a normal rate until the epithelium has grown across the anterior surface of the incision. Any removal of corneal epithelium causes an alteration in the appearance of corneal stromal cells which are an important source of fibroblasts.

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We wish to express our appreciation to Miss Carmen Marcos for her technical assistance.

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REPORT ON THE DIATHERMY TREATMENT OF RETINOBLASTOMA*

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Retinoblastoma, a congenital malignant tumor of childhood, is bilateral in at least 25 to 30 percent of the cases. The involvement of the second eye may be present at the first visit to the ophthalmologist or may not make itself manifest for several years. In these bilateral cases, practically every ophthalmologist believes in enucleation of the more involved eye. In regard to the second eye, methods of attack other than enucleation must be considered. The most frequently used are irradiation, chemotherapy, and diathermy, or a combination of any of these.

The first, irradiation, has been employed for many years in various forms, such as posterior portal X rays, radon seeds implanted in the sclera, radioactive tantalum wire placed in the orbit, and cobalt discs sewed to the sclera over the lesion. All of these have had some measure of success but have often been attended by late diastrous results from too heavy dosage.

The second method, that of chemotherapy, has been effectively employed by Reese and his associates,[1] using triethylenemelamine in conjunction with lighter doses of X-radiation than were formerly used.

The third method, diathermy, was first used by Weve[2] in 1930. Reports of its use appear rarely in the literature. Weve, who has employed it in more cases than anyone, is not too enthusiastic about it in retinoblastoma believing it should be used only in small tumors not too near the optic nerve. Others[3,4] have reported successful results but the follow-up periods have been very short. Joseph and Offret,[5] however, have used it successfully in two cases with a follow-up of one year and three years, respectively, and Perera[6] obtained an excellent result in a case followed seven years.

At the Massachusetts Eye and Ear Infirmary, we have employed it in eight cases. In six of these, the results have been excellent, the follow-up period being from two to 16 years. In the other two, the method failed to destroy the tumor. All patients had had one eye enucleated with pathologic confirmation of the clinical diagnosis.

TECHNIQUE

The technique is fairly simple. The sclera is bared over the lesion, detaching recti muscles if necessary. It is important to localize

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the tumor, or tumors, accurately. This can best be done by indenting the sclera near the lesion with a flat nonperforating diathermy electrode while observing the tumor with the Schepens' ophthalmoscope. When the edge of the lesion is located, a superficial mark is made on the sclera by the diathermy current. Additional marks are made all around the tumor under direct ophthalmoscopic control. When the tumor is completely surrounded, two-mm. perforating electrodes are used in the center of this area. Usually a 30-ma. current is used and the needles allowed to remain eight to 10 seconds. A number of perforations are made so that the area is thoroughly covered.

The reactions to this procedure consist in swelling of the retina and the appearance of hemorrhages on its surface. In certain eyes, when the electrodes have penetrated through the tumor into the vitreous, air bubbles will be seen ophthalmoscopically but these will be gone the next day.

During the next few days, the tumor takes on a gray appearance, the hemorrhages become more extensive, and vitreous opacities appear. Then the tumor begins to shrink and the hemorrhages become less. Eventually a flat, scarred atrophic area is left, surrounded by pigment. The vitreous opacities become minimal. The eye tolerates the procedure extremely well.

This method of diathermy coagulation offers certain advantages. It is simple and less complicated than the implantation of radon seeds or cobalt discs. It is less time-consuming than the combination of chemotherapy and X-radiation and certainly less hazardous in respect to possible bone marrow changes and X-ray damage. It can be repeated if necessary. Its disadvantages are that it is not applicable in certain inaccessible tumors near the optic nerve and in very large tumors protruding out into the vitreous. Also, in seeding of retinoblastoma into the vitreous or on the iris it should not be attempted. Weve calls attention to the danger of tumor cells escaping into the orbit through openings in the sclera if perforating diathermy is used and for this reason he prefers surface diathermy. So far we have not encountered this complication in the small series reported even in those cases in which the tumor continued to grow after treatment. It would seem necessary to employ perforating needles to reach the growth although in small flat tumors perhaps a surface cooking might suffice to destroy the tumor's blood supply.

Report of cases

Case 1

L. H., a white boy, aged seven years, was first examined February 20, 1937. The vitreous of the right eye was filled by a large tumor. The left fundus showed a small tumor nasally at the equator. Vision: O.D., nil; O.S., 20/20. Family history negative. Clinical diagnosis: retinoblastoma O.U.

On April 17, 1937, the right eye was enucleated. Pathologic diagnosis was retinoblastoma (nerve normal). X-radiation was given to the left eye over a period of six weeks (total 8,000 r) and regression of the tumor was noted.

April 9, 1938. Tumor in the left eye began to grow again and another course of X rays was given over a six-week period (8,000 r) with obvious regression.

September 9, 1939. Cataract formation and damage to the skin of the left temporal region was noted from excessive X-ray therapy.

March 27, 1940. Tumor again became active and, since further irradiation was contraindicated, it was decided to employ diathermy.

May 9, 1940. Operation left eye (Dr. Virgil Casten). The tumor was accurately localized and was thoroughly cooked by flat and perforating diathermy with subsequent regression.

June 20, 1945. The visual acuity had now decreased to 20/200 because of the lens opacity, so linear cataract extraction was performed with good result.

June 1, 1947. Patient has been attending college. Vision: O.S., 20/50 with correction. Numerous vitreous opacities.

December 13, 1956. Vision: O.S., 20/30—1. Fairly full field. Fundus shows scarred areas from diathermy. There are numerous vitreous opacities. The patient is perfectly well except for the effects of the radiation burn to his skin, which is still troubling him. Follow-up period: 16 years.

Case 2

C. T., a white girl, aged 11 months. On June 9, 1948, the first examination showed large tumor in the right eye and small tumor in the left eye, twice the size of the disc, at the 11-o'clock position in the periphery. Family history negative. Clinical diagnosis: retinoblastoma, O.U.

June 12, 1948. Enucleation right eye. Pathologic diagnosis: retinoblastoma (nerve normal).

June 16, 1948. Operation left eye (Dr. Virgil Casten). The tumor was localized and treated with perforating electrodes. The convalescence was uneventful and no further growth of the tumor was noted.

March 1, 1952. Vision: O.S., 20/40 with E chart. Media clear.

September 12, 1956. Vision: O.S., 20/25+1.

October 1, 1957. Vision: O.S., 20/20. Fundus normal except for scarred areas. The patient is in excellent health. Follow-up period: Nine years.

CASE 3

R. K., white boy, aged 15 months. On February 10, 1949, a large tumor was noted in the right eye. The left eye was normal. The family history was negative. Clinical diagnosis: retinoblastoma, O.D.

February 11, 1949. Enucleation right eye. Pathologic diagnosis: retinoblastoma (nerve normal).

June 22, 1949. The patient had been examined at monthly intervals and on this date three small separate tumors were noted near the periphery of the left fundus at the 10-, 12-, and 6-o'clock positions, each appearing about the size of the disc.

June 23, 1949. Operation left eye (Dr. Edwin Dunphy). Each tumor was treated by perforating diathermy with marked subsequent regression.

October 1, 1955. Vision: O.S., 20/25. Media clear.

November 1, 1956. Vision: O.S., 20/20. Fundus normal except for the three scarred atrophic areas in the periphery. Follow-up period: Seven years.

CASE 4

J. S., a white boy, aged 13 months; when first seen on January 20, 1955, there was an extensive tumor in the left eye and three small tumors in the right eye, one above the disc near the equator and two others near the ora serrata about two o'clock. Family history negative. Clinical diagnosis: retinoblastoma, O.U.

January 21, 1955. Enucleation left eye. Pathologic diagnosis: retinoblastoma with extension through the sclera near the disc. The optic nerve was involved but not beyond the cut end.

January 26, 1955. X-radiation to left orbit begun. Single anterior portal, 200 kv. Thirteen treatments of approximately 300 r each for a total 3,970 r. No orbital growth noted subsequently.

February 12, 1955. Operation right eye (Dr. Charles Schepens). Perforating electrodes were used for the larger tumor above and nonperforating diathermy was applied to the two smaller tumors near the ora. No further growth of the tumors was noted at subsequent examinations.

January 10, 1956. Child apparently healthy. Media clear. Seems to see normally. Orbit, O.S., normal.

January 20, 1957. Doing well. No recurrence of the tumor in the right eye or in the left orbit. Follow-up period: Three years.

CASE 5

B. R., a white girl, aged 15 months, when seen on June 23, 1955, a large tumor occupied the vitreous in the right eye, pushing the lens-iris diaphragm forward. The cornea was partly opaque. The left fundus showed a fairly large tumor in the periphery at the 10- to 11-o'clock positions and one small tumor near the ora at the 9-o'clock position. Family history negative.

June 24, 1955. Enucleation right eye. Pathologic diagnosis: retinoblastoma with extension into choroid, iris, and anterior chamber. Optic nerve involved but not beyond cut end. No extension into orbit.

June 27, 1955. Operation left eye (Dr. Robert Brockhurst). Each tumor was treated with perforating electrodes.

November 23, 1956. Reactivation of one of the smaller tumors was noted. Diathermy treatment was repeated, using perforating electrodes.

February 6, 1957. Looks fine. No sign of recurrence. A few vitreous opacities.

August 9, 1957. Continues to do well. No recurrence. Follow-up period: Two years.

CASE 6

W. Q., a white boy, aged 11 months on January 26, 1956, showed an extensive tumor left eye filling globe. Small tumor right eye upper nasal quadrant. Family history: mother had unilateral retinoblastoma with enucleation 25 years ago. Clinical diagnosis: retinoblastoma, O.U.

January 27, 1956. Enucleation left eye. Pathologic diagnosis: retinoblastoma (optic nerve normal).

February 1, 1956. Operation right eye (Dr. Richard Chapman). Perforating and nonperforating diathermy. Uneventful convalescence.

January 29, 1957. No recurrence of tumor. Media clear. Apparently well child.

November 18, 1957. Doing well. No sign of recurrence. Follow-up period: One year and nine months.

CASE 7

E. M., a white girl, aged seven months, was first seen on April 21, 1948. A large gray mass filled the vitreous of the right eye and there was a smaller tumor in the left fundus about 12 o'clock near the periphery. Family history negative. Clinical diagnosis: retinoblastoma, O.U.

April 24, 1948. Enucleation right eye. Pathologic diagnosis: retinoblastoma (nervehead involved but not beyond cut end of nerve).

May 29, 1948. Implantation of radon seeds in sclera over the lesion in the left eye (Dr. Garret Sullivan). Three gold seeds each one-MC. in strength were used.

June 11, 1948. Some regression of tumor noted.

August 6, 1948. No further growth of tumor but two new seedings observed, one in nasal periphery and one almost two disc diameters temporal to the macula.

September 1, 1948. Diathermy (Dr. Charles

Schepens) applied to the fresh tumor areas under direct ophthalmoscopic contact. Regression of temporal tumor but nasal tumor recurred.

December 11, 1948. Another application of diathermy made. Regression noted for a while but recurrence took place.

May 28, 1949. Diathermy again applied but again recurrence took place. In view of persistence of the retinoblastoma, no more attempts at diathermy were undertaken but enucleation of the remaining eye was considered. General medical and neurologic work-up failed to reveal any evidence of metastasis.

November 4, 1949. Enucleation of the left eye. Pathologic diagnosis: retinoblastoma of nasal half of retina with invasion of sclera, choroid, ciliary body, and nervehead.

May 12, 1950. Admitted to hospital for sixth time for repair of socket, left eye, in which glass ball implant had shown tendency to bulge through lower part of conjunctiva preventing wearing of a good prosthesis. X-ray films of orbit showed marked increased density of sphenoidal ridge suggesting stimulation of bone from neoplasm. Therefore no extensive orbital repair was attempted, but glass ball implant was removed.

August 11, 1950. Increasing irritability; X-ray film shows defect in left lower orbital rim and a mass can be felt in the left lower lid.

December 15, 1950. Patient died. No autopsy.

Case 8

N. C., a white boy, aged six weeks, was first seen on March 19, 1954. The right eye contained a large white solid mass occupying the lower temporal equator. Left eye showed a small tumor just below the optic disc. Family history negative. Clinical diagnosis: retinoblastoma, O.U.

March 24, 1954. Enucleation right eye. Pathologic diagnosis: retinoblastoma (nerve normal).

March 31, 1954. Diathermy of tumor, left eye (Dr. Charles Schepens) done with great difficulty because of posterior location and smallness of orbit.

May 21, 1954. Recurrence of tumor noted. Because of difficulty of reaching the tumor, no further attempt at diathermy was made, but a course of nitrogen mustard was given. For a while tumor remained stationary, but then began to grow rapidly.

August 2, 1954. Enucleation left eye. Pathologic diagnosis: retinoblastoma posterior with partial destruction from diathermy (nervehead normal). A new independent retinoblastoma was found in the anterior retina.

July 12, 1957. Both sockets clean, no evidence of local recurrence. For the last three years has done very well. General examination reveals no evidence of distal metastasis.

Comment

In Case 1 diathermy was successful after X-ray therapy had failed to halt the growth of the tumor. However, the method of X-ray therapy employed in this case was not in accordance with modern technology.

In Case 2 the tumor was fairly small and easily accessible. The result was excellent.

In Case 3 the tumors in the second eye did not make themselves manifest until four months after enucleation of the first eye, which illustrates the importance of continued observation in cases of retinoblastoma. In spite of the fact that these were separate tumors, the eye tolerated the diathermy extremely well and a perfect result was obtained.

In Case 4 there were also three separate tumors in the remaining eye, all of which were effectively eradicated by diathermy.

In Case 5 there were two tumors in the remaining eye, one of which showed reaction after the first diathermy treatment, but regressed after the second application.

In Case 6 the diathermy treatment apparently was efficacious although the follow-up period is a little less than two years.

Cases 7 and 8 were failures. In Case 7, after radon-seed implant had apparently halted growth of the tumor, two new tumors appeared. These were treated by applications of diathermy on three separate occasions but without avail and the remaining eye was enucleated. Fatal termination ensued from orbital and distal metastasis. Case 8 presented the difficult problem of attacking a small tumor adjacent to the optic nerve in an infant's orbit where there was very little room. After one unsuccessful attempt it was decided to use chemotherapy which also failed to stop the growth and eventually enucleation of the remaining eye was performed.

Conclusion

In cases of bilateral retinoblastoma, after enucleation of the more advanced eye, diathermy to the remaining eye is a method of treatment which offers some hope when the tumor is small and accessible. Accurate localization and destruction of the tumor under direct ophthalmoscopic control are essential. It is too early to say if this method of treat-

ment is as effective as the combination of chemotherapy and X-radiation, or other methods, since not enough cases have been reported with sufficiently long follow-up periods. In the eight cases done here it was most successful in six. It would seem contraindicated in very large tumors, small tumors near the optic nerve, or in eyes with seedings in the iris or vitreous. It must be emphasized that retinoblastoma may have multiple origins. Therefore thorough and repeated examinations of the fundus must be carried out to be sure no new growth is missed.

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POSTOPERATIVE HYALOID ADHESIONS TO THE CORNEA*

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During the first few weeks following uncomplicated intracapsular cataract extraction, a situation may develop that is extremely unpleasant. If this is not recognized early and treated promptly disastrous results will surely follow. I refer to adherence of the intact hyaloid membrane to the back of the cornea. That this is not infrequent is evidenced by the fact that it occurred in 12 of the last 300 of my private cases in which no trouble was encountered at operation nor within the next few days. About half of the patients had combined extractions, the other half round-pupil with peripheral iridectomy or iridotomy. In all cases a fornix-based flap was used, with four or five mild chromic, postplaced sutures. Air was injected into the anterior chamber and a miotic instilled. None of the patients had flat or shallow anterior chambers during their seven-day stay in the hospital. My records show that eight of the 12 cases developed shallow or flat chambers rather late—the earliest on the 11th postoperative day, the latest on the 29th day, with an average of 18 days.

My reason for writing this article is that, in spite of the fact that there have been a few papers touching on the subject, the complication is often unrecognized until irreversible changes in the cornea have taken place. Reese[1] called attention to this situation in an excellent article in 1948. Brandon Leahey,[2] in 1950, also discussed the complication at length. Rodman Irvine[3] described adhesion of fragments of the hyaloid to the cornea and named it the vitreous syndrome. However, this occurs months or years following round-pupil extraction.

Since two thirds of the patients with hyaloid adhesions had shallow or flat chambers, it seems worth while to discuss briefly why these occur. Many ophthalmic surgeons believe that only a leaky wound causes these, and no doubt a very high percent of primary shallow chambers are due to a leak. How-

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ever, those that occur late are probably caused by some other factor. Reese intimated in his paper that this might be true but did not discuss it further. Leahey states,[2] "The main means of prevention, of course, is to achieve rapid re-establishment of the anterior chamber after operation." Villaseca[4] postulated that late shallow or flat chambers are caused by the forward thrust of the vitreous, swollen through inbibing aqueous and pushing the iris diaphragm forward, emptying the aqueous through the drainage angle. I am convinced that the chief factor in late emptying of the anterior chamber is caused either by vitreous swelling as Villeseca supposes or by aqueous filtering back and surrounding the vitreous, thus detaching it from behind and pushing it forward.

My reasons for this belief hinge on two clinical observations:

The first is that following retrobulbar injection of procaine, adrenalin, and hyaluronidase, occasionally the anterior chamber will form and assume its normal depth. This would occur from retraction of the swollen vitreous as the eye softens.

The second is that a posterior sclerotomy through the pars plana will sometimes evacuate aqueous humor rather than vitreous.

Whatever the reason, the condition must be recognized and dealt with rather promptly. There is no difficulty whatever in diagnosing flat or shallow anterior chamber. Often it is most difficult, however, to know whether the hyaloid is adherent when the vitreous is herniated and pushed against the cornea and the anterior chamber is of normal depth. Usually the striae in the cornea disappear within two or three weeks. In the occasional case where the cloudiness of the cornea fails to improve or becomes denser one can be sure that something has disturbed the integrity of the corneal endothelium. This usually occurs just above the center of the cornea. The cornea is clear in the lower part and through this area it may be seen by the biomicroscope that the intact hyaloid is bulging forward but it is impossible to see through the cloudy area to note whether it is attached. In this event one may take for granted that something is disturbing the endothelium, and if cornea guttata is not present it may be assumed that it is the hyaloid. Strangely enough, if the hyaloid is ruptured, the back of the cornea is very seldom disturbed by being constantly bathed with vitreous. I have seen only one eye—that of an extraction with round pupil in which formed vitreous was lost—that showed in later years the exact picture of cornea guttata with some corneal edema and evanescent bullous keratitis. Leahey[2] states that he has seen three cases of bullous keratitis caused by free vitreous in contact with the cornea, but does not mention the condition of the endothelium.

Why does the hyaloid attach to some corneas with which it comes in contact and fail to do so in others?

It does not seem likely that an intracapsular extraction can be done without some injury to the corneal endothelium. Even if the cornea is held forward and the lens slid out without lens or instrument touching its back surface, the endothelium must be stretched and probably broken where the cornea is buckled. Any one who has watched pictures of tissue cultures of epithelium from nasal mucosa perfused with normal saline can imagine its devastating effect on the endothelium of the cornea. This raw surface caused by the trauma of operation is a fertile field for adherence of the intact hyaloid in persons who regenerate endothelium slowly or imperfectly. If the vitreous is thrust forward against such a cornea the hyaloid may adhere quickly and the longer apposition exists between the two surfaces, the denser the adhesion becomes.

The best treatment for this complication is prevention. Careful suturing of the wound is essential and in primary flat chambers the leak must be repaired. Unfortunately there is no way I know of to prevent the late occurrence of a flat anterior chamber or a hyaloid approximation to the cornea in a chamber of normal depth. Reese[1] advises that

the patient be placed flat on his back, the pupil dilated to allow the vitreous to drop back, then powerful miotics instilled to keep it in place. Weisel and Swan[5] believe that late loss of the chamber is due to adhesions between the hyaloid membrane and iris. They report remarkable success by use of strong mydriasis to separate the synechias, thus permitting aqueous to come forward into the anterior chamber.

I have tried both methods without much success.

Large doses of Diamox have been ineffectual in my hands.

Air can be injected into the anterior chamber as an office procedure. If the needle is seated firmly on the syringe so that one large bubble enters through the puncture in the cornea previously made with a needle knife, it is a simple matter to see whether the vitreous is pushed back completely, or that an adhesion to the cornea remains. In case this occurs, the adhesion must be broken with a spatula. Unfortunately in most of the cases with flat chambers when the air is absorbed the chamber is flat again. The only remedy in this situation is to do a posterior sclerotomy through the pars plana, evacuate considerable of the contents of the posterior segment, whether it be aqueous or vitreous, and inject air into the anterior chamber through a previously prepared puncture. If the puncture is not made before fluid is evacuated the eye is so soft that it makes the puncture difficult.

Posterior sclerotomy properly done is a harmless procedure, despite the fact we were taught it should only be done in blind eyes or in grave emergencies such as choroidal hemorrhage. My method is to make an incision through conjunctiva and fascia five mm. from the limbus, make a T-shaped coagulation of the underlying ciliary vessels with diathermy, thrust a Graefe knife through the sclera and ciliary body, turn the knife, and cut down through the T. After evacuation of considerable of the contents a suture or two is placed through conjunctiva and episclera to close the wound. Air is forced into the anterior chamber until it is quite deep and 10-percent pilocarpine is instilled.

The late treatment of hyaloid adhesions in my hands has not been very satisfactory because the cornea becomes scarred within eight or 10 weeks and when the adhesion is broken with a spatula a tag will usually remain on the back of the cornea; and the endothelium is permanently destroyed in the area. Every case of intracapsular extraction should be examined with the slitlamp microscope each postoperative visit for several weeks and persistent cloudiness of the cornea regarded with suspicion. If the hyaloid is intact and bulging far forward as viewed through the clear cornea, immediate steps should be taken to put the vitreous back in place. In my opinion posterior sclerotomy with air injection into the anterior chamber is the procedure of choice.

Summary

Adhesions of the anterior hyaloid membrane occurred in four percent of 300 uncomplicated intracapsular cataract extractions. Eight of these had late loss of the anterior chamber, four had chambers of normal depth. Normally cloudiness of the cornea disappears completely within two or three weeks after operation. If the striae continue or increase in a cornea that has had no evidence of corneal guttata, if the hyaloid is intact and can be seen bulging well forward through the clear cornea below, even though it is impossible to see the adhesion through the cloudy cornea, the surgeon has strong evidence that the anterior hyaloid is in contact with the back of the cornea and is adhering to it. He should take immediate steps to remedy this situation before a permanent opacity of the cornea occurs. Air injection will sometimes effect a cure, but often this procedure must be combined with posterior sclerotomy.

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A CONGENITAL ANOMALY SIMULATING TUMOR

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The developmental complexes formed in the anterior segment separately and jointly by the iris, ciliary body, lens, and retina are of great interest and frequently of practical importance. The causes lie in two fields of pathology—the less common developmental anomalies and postnatal acquired processes, especially from physical injury. Clinical manifestations usually take courses peculiar to each origin, but exceptions are encountered. Considerable difficulty concerning diagnosis and management may arise in the individual case.

The following report tells the story of an iris-ciliary-body-retina complex within the developmental anomaly field. Only hindsight provided the correct diagnosis and showed therapeutic possibilities.

Case report

History

The history was supplied by the referring physician. A five-year-old girl (full-term baby) presented a convergent left eye which had always been thought sightless. About six weeks before the initial examination the patient noticed she could see with the left eye—an event thought to be a miracle. No history of injury, inflammation, pain, or familial eye disorder was established.

Examination

Examination of the left eye (E 53-25) showed in a five-year-old otherwise healthy girl a convergence of about 30 degrees, Priestly-Smith method. A brownish to black mass mesially behind and possibly in the iris applied to the lens. The lens was cataractous and displaced toward the temporal, 3-o'clock position. Fundus details were not supplied. Intraocular pressure was not elevated. Transillumination was inconclusive. Following several examinations the left eye was suspected of harboring a tumor in the anterior segment. The right eye functioned normally and appeared to be normal in every way.

Laboratory examinations

Gross examinations showed: volume, six cm.; weight of globe, 4.6 gm.; measurements: horizontal, 20.5 mm., vertical, 21.5 mm., anterior-posterior, 21.5 mm. The globe was well proportioned and appeared to be that of a child except for a bulge of seven-mm. in diameter in the region of the attachment of the inferior oblique. The pupil measured four mm. and was somewhat off round and eccentric as the temporal half of the iris was somewhat displaced forward. Anterior chamber deep. Within the temporal half of the pupil the lens appeared tilted and the mesial edge rotated posteriorly as well as pushed temporally. An optic nerve present, measured two mm. in length.

The eye was fixed in formol and later opened horizontally. The cornea was normally thick and the anterior chamber appeared deep. The anterior surface of the iris appeared uniformly brown and the temporal side bulged because of a yellowish opaque lens about five-mm. thick in anteroposterior diameter, and displaced as noted. The ciliary body-lens angle was deeply pigmented. The lens appeared to be adherent to the temporal iris and ciliary processes. The vitreous was mostly fluid and supported a few strands extending from the posterior retina to the region of the lens. The retina was in position throughout. Vessels on the disc appeared dilated; the macula area was not remarkable.

The macroscopic appearance of the specimen on the slide showed the lens displacement and extraneous tissue behind the iris on the mesial side.

Microscopic findings may be somewhat briefly summarized: The cornea showed a pannus and a few deep stromal vessels. The angle was open and contained a few cells and considerable pigment in the trabecula. Schlemm's canal was open and con-

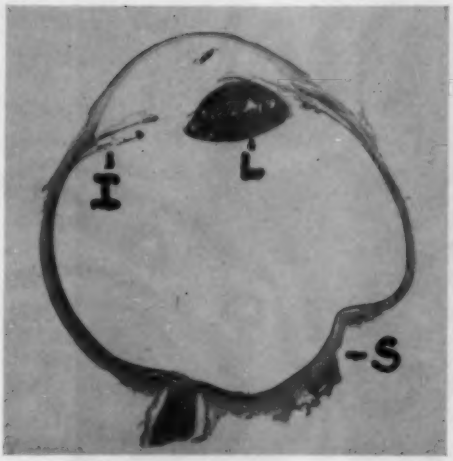

Fig. 1 (Heath). Whole eye (×2). (L) Lens displaced. (I) Iris-ciliary-body-retina complex. (S) Scleral staphyloma.

Fig. 2 (Heath). Mesial angle (×18). (R) Retinal tissue with cysts. (I) Iris pigment layer with cysts. (CB) Cystic ciliary body. (Z) Interrupted zonule. (V) Vitreous boundary.

tained some pigment, apparently of the melanin variety. The root of the iris extended from the ciliary body, contained considerable pigment and a few clump cells, and a few intra-epithelial cysts.

A few balls of pigment and flocculi and cells lay behind the iris near or in the pupillary space. A lens-iris synechia was well developed. The mesial root of the iris was attached to a long peninsula of anomalous cystic retinal and ciliary body tissues extending into the pupillary zone, during life, no doubt, pushing and tilting the lens toward the temporal side.

The intra-epithelial cysts contained fine granular debris, red discoids, and rare blood cells. The cysts formed by the cilioretinal epithelium contained numerous blood vessels, some large capillaries, vitreal strands, few red blood cells, and amorphous debris. A fenestrated membrane on the inner aspect of the ciliary body was continuous with that from the pigment epithelium of the retina and coupled with Bruch's membrane. The choriocapillaris as it approached the ciliary body appeared on both sides of Bruch's membrane. Larger vessels were closely applied to the outer side. The retinal pigment layer

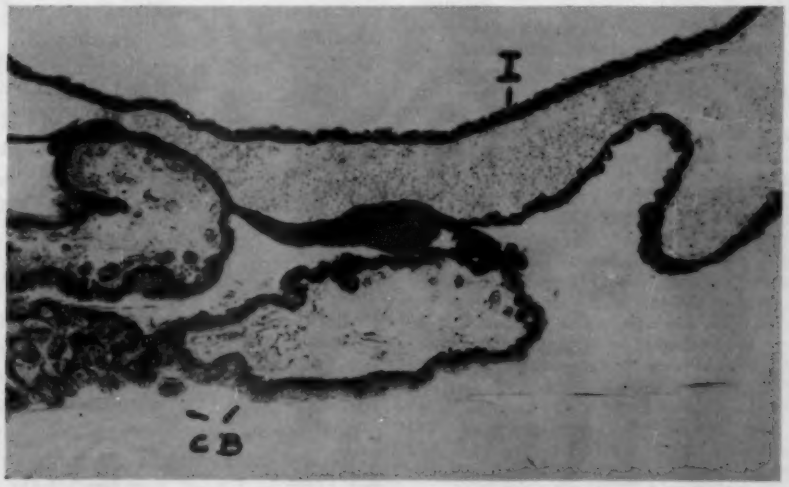

Fig. 3 (Heath). Detail of iris (I) and ciliary body (CB) cyst formations (×70).

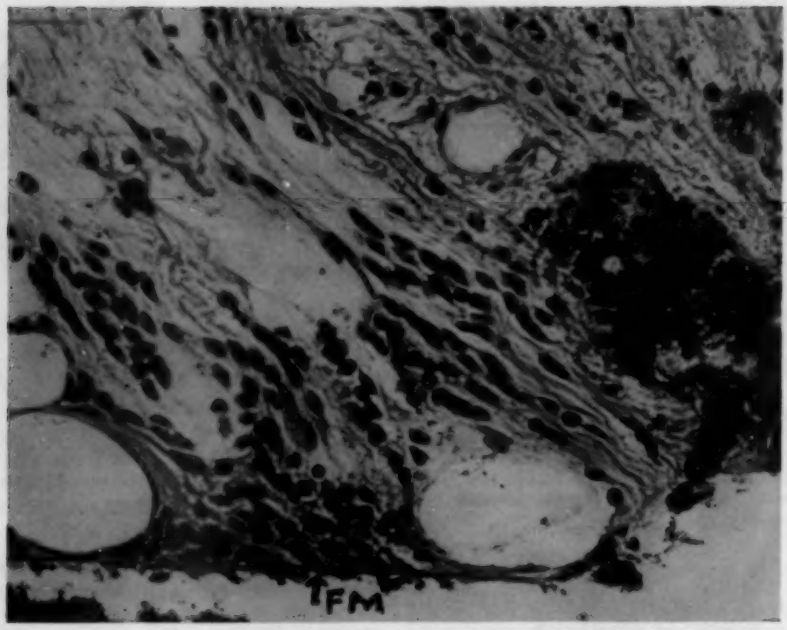

Fig. 4 (Heath). Detail of retinal component (×300). (FM) Fenestrated membrane.

made the transition to unpigmented ciliary epithelium on the tongue or peninsula complex.

The ciliary body appeared to be rather small and partly differentiated and loose and contained pigment scattered in the anterior aspects. Large vessels here showed margination. The pars plana was nearly nonexistent on the mesial side, and apparently had contributed heavily to the aberrant tissue effecting a displaced lens. The mesial side of the choroid showed more vessel content than the temporal. The lens thinned out somewhat mesially and the posterior surface in some sections showed some dishing inward.

Posterior synechia were rather broadly attached to the lens capsule. The whole lens was displaced to the temporal side; fluid clefts were present; bow cell nuclei sharply reduced; epithelial nuclei extended abnormally posteriorly. The lens stained in a diffuse cataractous manner. The vitreous boundary occupied its usual position behind the lens.

A hyaloid remnant could be traced from the mesial aspect of the lens to the mesial side of the nerve head. The posterior retina apparently contained the usual number of ganglion cells in the macula, but these rapidly tapered off, especially mesially. Some ganglion cells appeared over the ciliary body. The nerve head was reduced in diameter and glial columns were irregular. The sclera was thin on the entire temporal side, and contained an area of staphylomatous bulging near the insertion of the inferior oblique muscle.

Discussion

The iris contribution to the cystic aberrant tissue was mostly pigment epithelium. Cyst formations from iris, ciliary, or retinal types of tissue increase in size as the tongue reaches toward the axis of the globe. It is possible that atypical formations of ciliary processes which normally begin at the 60- to 70-mm. stage held and dragged the iris pigment inward. The displaced iris epithelium formed flocculi but not ectodermal muscle. The ciliary processes at about the 75-mm. stage are on the lens and should have withdrawn safely away by the fifth month and this gives us some idea of timing. Or if held by atypical persistent tunica vasculosa lentis the ciliary-iris structures would by growth follow closely and become attached to the lens, and years later exert pressure by developing cyst formations. The persistent myaloid artery which does not carry blood and extensive lens attachments if present early had now, five years later, disap-

peared. The suspensory zonule of the lens and the ciliary muscle appear during the third month normally, therefore, interacting defects in the former could contribute toward attachments to the lens. When the margin of the optic cup is growing forward, at the 48- to 50-mm. stage, the retina is redundant and by position could become incorporated into atypical differentiations with the ciliary processes at larger stages.

That the anomaly we see is developmental and not a metaplasia is indicated by collateral findings of persistent hyaloid artery, the nature of the lens changes, and the defects not limited to the anterior segment which include defective development of the posterior sclera in the region of the inferior oblique (abortive coloboma).

We can only speculate upon the exact mechanisms initiating the abnormality. The interval of five years since birth has been long enough to mask and resolve the actual interplay of obstruction and adhesive forces causing the display we have described above. Certainly the changes are developmental as opposed to inflammatory origins, and probably extend over the organic, neofetal, and fetal periods.

Because of the well-developed posterior segment, especially the retina, the question of therapy and clinical procedure are important. The first consideration is diagnosis. An anterior segment anomaly was suggested by the nature of the cataract, size of eye, muscular imbalance, and absence of inflammation, and the rate of growth. The cystic nature of the growth would be difficult to establish by inspection, but should be suspected from the displaced lens. The age of the patient is against malignant melanoma and also retinoblastoma. In consequence of hindsight, the surgical procedure would seem to be iridectomy and attempt to remove the underlying cystic structure. Not only would this offer the best avenue of attack, but it also would provide material to clinch the diagnosis.

Fig. 5 (Heath). Posterior segment (×8) shows good differentiation.

Summary

The convergent left eye of a girl, aged five years, was thought to be blind from cataract of congenital type. Spontaneous restoration of partial vision occurred. Examination showed a pigmented mass pushing the cataractous lens toward the temporal side partly uncovering the pupil space. Laboratory study of the eye showed an iris-ciliary body-retinal complex evolving from a developmental anomaly. Expansion of the aberrant tissue which lay behind the mesial iris was by growth and multiple cystic formations.

LAMELLAR KERATOPLASTY FOR HERPES FEBRILIS ULCERATION OF THE CORNEA*

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Herpes febrilis infections of the cornea appear to have increased in frequency and severity during recent years. Some respond promptly to therapy. Others provide special therapeutic problems to the ophthalmologist. Frequent recurrence, resistance to therapy, extension to the corneal stroma, and chronic ulceration are common. In the past 10 years there has been a definite increase in the frequency of chronic herpetic ulceration of the cornea, especially in the types which lead to ulceration and perforation.

Newer methods of therapy with corticosteriods and antibiotics partially account for the increase in these infections, and their complications. It has been shown[1] that such therapy may lead to chronicity and secondary infection of the ulcers by fungi.

The therapy of dendritic ulceration, disciform keratitis, and disciform ulcerations often is unsatisfactory. The most difficult complications to treat are herpetic iritis with its severe pain, and glaucoma which occurs in a large percentage of cases. Both are resistant to the usual treatment.

We have described[2] some of the types of herpes febrilis cases which come to surgery, and attempted to classify them with regard to prognosis and surgical results.

This report will discuss the types of corneal herpes cases which are suitable for lamellar keratoplasty, the technique used by us, the immediate and late complications, and the eventual outcome of such surgery.

Dendritic keratitis is the most common form of corneal herpes; its characteristic type of ulceration is easily recognized. The treatment of such ulcers is usually but not always successful, and is fairly well established. Recurrences are common.

Some cases tend to persist longer, resist therapy, and extend into the stroma to result in disciform keratitis, which persists long after the surface ulceration has completely healed. Other cases fail to heal and there is extension of the ulcer into the stroma, with marked resistance to medical treatment. Such lesions often are accompanied by a severe and painful iritis, with or without secondary glaucoma. Cultural studies of these deep ulcers are usually negative; some are due to secondary bacterial or fungal infections. Isolation of the herpes febrilis virus from such ulcers is uncommon. Perforation is not unusual in the deeper ulcers. Vascularization of the cornea invariably commences in the later stages and is of the superficial and deep types.

Therapeutic lamellar grafting is indicated in the following types of cases:

1. Those with chronic superficial ulcerations which fail to heal after two or three months' treatment.

2. Those with deeper more extensive ulcerations which fail to respond within two or three months to a variety of methods of treatment.

3. To prevent frequent recurrences of dendritic ulcerations.

4. In chronic disciform ulcers which have perforated.

The contraindications to lamellar keratoplasty in these types of cases are:

1. *Secondary infection by bacteria or fungi.* Bacterial infection is controlled by determination of the antibiotic sensitivity of the organisms and giving appropriate therapy. Fungal infections can be treated with mycostatin ointment (50,000 u./gm). five to six times a day. This is rarely effective and it

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is usually necessary to perform a penetrating keratoplasty rather than a lamellar one although the size and depth of the secondarily infected corneal lesion is a determining factor. In ulcers involving most of the cornea after the infection is brought under control a purse string conjunctivoplasty is probably best.

2. *Glaucoma.* Every attempt should be made to control the pressure before considering surgery. In those with uncontrolled pressure the removal of necrotic tissue at the time of keratoplasty often results in amelioration of the intraocular inflammation, and subsidence of the glaucoma.

3. *Iridocyclitis.* A reasonable degree of iridocyclitis is always present during the active phase of ulceration, and resists treatment. Corticosteroid therapy usually is of no value in such cases. The iridocyclitis usually subsides following lamellar keratoplasty, and it is reasonable to suppose that the necrotic corneal tissue may favor such inflammation.

Technique

In my opinion lamellar keratoplasty is preferable for many of the chronic herpes febrilis ulcers of the cornea. The corneal tissues usually are diffusely inflamed, soft, and vascular, and do not hold sutures as well as normal cornea; therefore it is risky to perform a penetrating keratoplasty. Central, rather circumscribed ulcers, in which the surrounding cornea is tough and relatively uninflamed, are best treated by partial penetrating keratoplasties.

Anesthesia

The usual preoperative sedation, orbicularis akinesia, and retrobulbar injection are given to anesthetize the eye.

Procedure

Four-0 black silk sutures are placed in the superior and inferior rectus muscles for fixation. Any of the types of trephine is suitable for this procedure, but I prefer the Katzin or Franceschetti type. The trephine

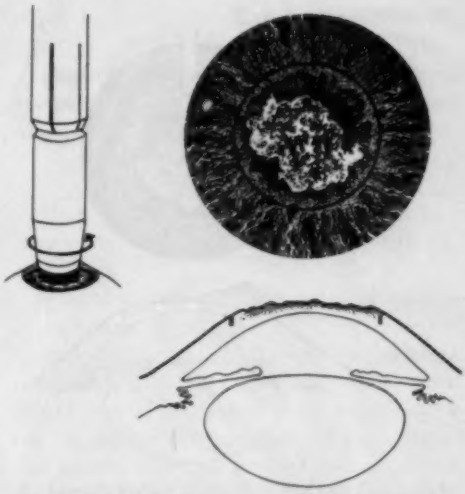


Fig. 1 (Hogan). The trephine should be of such size that it encompasses the ulcerated area.

should be of such size that it encompasses the ulcerated area (fig. 1). The guard is set so that the cutting blade will penetrate to about one-half the thickness of the patient's cornea.

After trephining the recipient eye the edge of the portion to be excised is retracted slightly with a Castroviejo corneal forceps and the peeling of the lamella is initiated by making a short incision with a Bard-Parker knife. The tip of an Elschnig cyclodialysis spatula is inserted into this area and used to separate the lamella from the remainder of the cornea. To accomplish this the blade is pushed forward between the lamellae slowly by twisting motions until it completely separates the diseased area from the remainder of the cornea (fig. 2). This method of separation of the lamella is of advantage because of its simplicity and the greater ease with which one can stay in the same plane.

After removal of the first layer of necrotic tissue it may be seen that additional lamellae must be removed. The trephine guard is readjusted and a slightly deeper cut made. As an alternative a shallow groove can be made at one edge of the trephined area with a Bard

Fig. 2 (Hogan). The blade is pushed forward between the lamellae slowly by twisting motions.

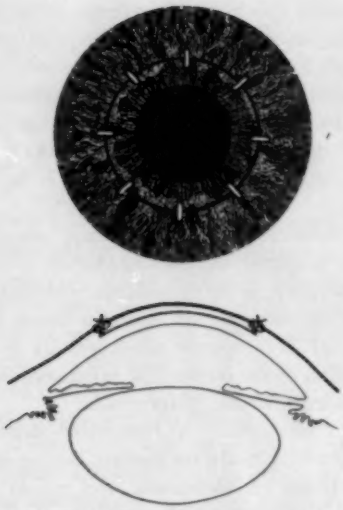


Fig. 3 (Hogan). Eight black-silk, 6-0 sutures are placed edge to edge.

Parker knife. Following this the Elschnig spatula again is used to separate a new lamella of tissue. This procedure can be repeated, even in perforated ulcers, down to Descemet's membrane. In those eyes with a descemetocele, or a perforation, one usually finds a plug of necrotic tissue at the base of the ulcer. This plug usually comes loose, leaving a two- to three-mm. hole into the anterior chamber. This finding does not preclude continuance with a lamellar keratoplasty. In other cases, after removal of most of the diseased tissue down to Descemet's membrane, one sees a two- to three-mm. area of gray haziness. In such a case the surgery is continued and in many instances this area clears.

Meanwhile, the donor eye has been soaked in ophthalmic Neosporin solution for one hour. It is wrapped in gauze, leaving the cornea exposed, for ease of handling. The trephine blade is adjusted so that it will cut through the desired depth of cornea, depending on the amount excised from the recipient eye. After making the cut, the donor button is separated from its bed with the spatula, as previously described. It is then sutured in place with eight 6-0 black silk-sutures, edge to edge (fig. 3). Atropine ointment and ophthalmic Neosporin ointment are instilled, and bilateral patches applied. A pressure dressing is applied to the operated eye.

Postoperative care

The eye is dressed daily, a pressure dressing being maintained for one month. The unoperated eye is uncovered on the third postoperative day.

The pupil is kept dilated, and Neosporin ointment applied to the lid margins daily for four or five days. The patient is allowed up on the fourth postoperative day, and home on the seventh. Antibiotic and corticosteroid preparations should be avoided, because of predisposition to fungal or other infections. Since glaucoma is a frequent accompaniment of the disease it must be watched for constantly in the postoperative period.

Iritis invariably accompanies the disease and its surgery, and the size of the pupil should be varied frequently to prevent synechia formation. Most often, however, the pupil already is partially fixed by preoperative synechias. In those without such adhesions, they frequently develop in spite of treatment.

Those eyes with grafts applied over perforations often have considerable edema of the cornea and graft, the area of perforation being easily discernible. After one to two months the perforation seals, and the edema gradually subsides. One must be on the alert in those patients with persistent edema to prevent secondary infection, and it is best to use an antiseptic regularly to prevent such infections.

Adhesions of iris to the area of perforation must be treated as in penetrating keratoplasties. It is best to free adhesions through a limbal incision with a spatula soon after this formation, usually during the third to fourth postoperative week.

Results

Table 1 shows the results obtained by performance of lamellar keratoplasty on nine cases of chronic herpetic ulceration of the cornea, with and without perforation.

One cannot evaluate such cases according to the usual standards. Under the desperate circumstances these cases present, the surgeon is fortunate to save the eye. Three cases (Cases 1, 4, and 5) had perforations of the central cornea, with considerable surrounding keratitis. The grafts were quite edematous for some months but eventually became quiet and clearer. Vision was improved considerably in one case, and was unchanged in the other two. These cases have not been followed long enough to determine the final acuity, but they are quiet. One patient (Case 3) was treated an inordinate time with antibiotics, and three months after a quite successful keratoplasty developed a Monilia ulcer at one edge of the graft, resulting in its destruction.

One case (Case 2) had a good early result with fairly clear cornea and graft. Six weeks postoperatively there developed a separation of the wound at one edge, with edema of the graft. This eventually healed, but four months later a severe glaucoma developed. After some time it was brought under control by medical measures. Vision is now much improved (10/200 on November 20, 1957).

Four cases (Cases 6, 7, 8, 9) all obtained successful grafts, developed quiet eyes, and improved vision.

Complications

Many complications accompany such surgery early and late in the postoperative period.

Wound separation may occur early because of loosening of the sutures. They may loosen because of the soft tissues in the recipient cornea as a result of inflammation. Such separations at times may occur because of a rise in intraocular pressure. If the separation occurs in a case grafted over a corneal perforation, the graft usually becomes quite edematous. Control of the glaucoma and maintenance of a pressure dressing usually results in reattachment of the graft, and subsidence of the edema. Resuturing usually is not desirable.

Glaucoma is one of the commonest complications of the herpetic infection, and of the surgery. Some cases respond to Diamox, pilocarpine, and epinephrine solutions. Others resist all therapy, and one must be content with controlling pain, attempting to quiet the inflammation by oral corticosteroid therapy, as well as by local drops. The pressure often returns to normal gradually, as the inflammation subsides.

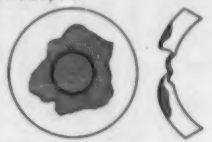
Iridocyclitis may persist after the surgery and resist all therapy. The pupil should be kept dilated most of the time, but not allowed to adhere to the lens in a dilated position. Oral corticosteroid therapy may be ordered, but rarely is of much benefit.

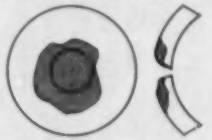
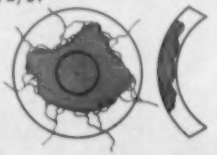
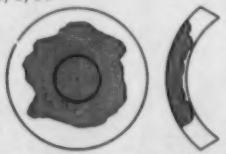
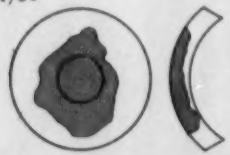
Secondary infection may occur. It has not been observed in our series, except in a late case which was overtreated with antibiotics. Those patients with persistent edema of the graft should be treated with antiseptic drops to prevent infection of one of the vesicles. Cultural studies should be done in the event of infection, and proper therapy instituted.

Iris adhesions to the graft or perforated

TABLE 1

RESULTS OBTAINED IN NINE CASES OF CHRONIC HERPETIC ULCERATION OF THE CORNEA

Name	Age (yr.)	Sex	Vision	History	Findings	Surgery	Results
1. R. T.	44	M	R. 20/20 L. H.M.	1953—L. E. Corneal herpes for 6 mos. 2/1/57—L.E. Dendritic ulcer with labial herpes. Progressive stromal involvement with ulceration.	7/2/57 L. E.  Necrosis with iritis and pain.	7/5/57—7.5 mm. lamellar keratoplasty. Small central perforation due to ulcer.	8/7/57—Wound separation. Congested hazy graft. Anterior chamber O.K. 9/28—Glaucoma. 10/26—Glaucoma controlled. Graft hazy. Vision—H.M.
2. F. C.	52	M	R. 20/20 L. L.P.	1932—L.E. Dendritic ulcer. 2/27/57—Dendritic ulcer. 3/15/57 Recurrence with progressive ulceration.	5/1/57 	5/4/57—7 mm. lamellar keratoplasty. Descemet's hazy.	6/15/57—V. L.E. 20/400. Wound poorly healed. 10/19/57—Glaucoma. 11/5/57—Graft clearer, glaucoma controlled. V. L.E.—C.F. 3'.
3. F. T.	50	M	R. 10/200 L. 20/20	1907—Age 2, R.E. Corneal ulcers, recurrences to age 12. Age 36, recurrent dendritic ulcers. Yearly thereafter. Recurred 10/56.	R.E. 10/56  Progressive ulceration.	12/27/56—7 mm. lamellar keratoplasty, to Descemet's.	1/22/57 Quite clear. 3/30/57 Monilia ulcer following antibiotic therapy. Hypopyon. 4/12/57—9 mm. keratoplasty. 5/25/57—Glaucoma, staphyloma.
4. J. H.	48	M	R. 20/20 L. L.P.	8/56—L.E. Dendritic ulcer. Recurrences with progressive ulceration.	L.E. 12/56 	1/11/57—8 mm. lamellar keratoplasty. 3 mm. hole in Descemet's.	Prolonged healing. 6/9/57—Diffusely hazy but quiet. Vision—L.P.

Name	Age (yr.)	Sex	Vision	History	Findings	Surgery	Results
5. E. B.	37	M	R. 20/30 L. H.M.	L.E. 10/3/56 Dendritic ulcers with recurrences.	12/27/56 Perforation.  No anterior chamber.	1/11/57—8 mm. lamellar keratoplasty. 2 mm. perforation in Descemet's.	Prolonged healing. 11/22/57—V. L.E. 20/200.
6. L. Mc.	36	M	R. H.M. L. 20/20	1/27/57—R.E. Dendritic ulcer with extension to deep stroma. No healing.	3/2/57 	3/11/57—7 mm. lamellar keratoplasty, to Descemet's membrane.	Prolonged clearing. 10/9/57—V. R.E. 10/200. Diffuse haze.
7. M. G.	37	F	R. C.F. L. 20/20	R.E. Onset age 5 yrs. Many recurrences; especially 1952–54.	7/8/54—Active ulcer R.E. No help with treatment. 	8/27/54—8.0 mm. lamellar keratoplasty. Descemet's O.K.	10/29/54—V. R.E. 20/200. (Always partially amblyopic). 8/56—No recurrence. Vision 20/200.
8. R. S.	67	F	R. 20/30 L. L.P.	1953—Dendritic ulcer left cornea 3 mos. 5/1/56—Recurrence of persistent ulcers, becoming deeper. Vision H.M.	5/1/56 	6/26/56—7.5 mm. lamellar keratoplasty. Descemet's slightly hazy.	8/56—Clear graft. Vision 20/50 with glasses.
9. J. S.	65	M	R. 20/40	9/52—Dendritic ulcer with recurrences to 1/54. Progressive ulceration thereafter.	1/54 	2/17/54—7.0 mm. lamellar keratoplasty. Descemet's O.K.	Slow improvement. No complications. 8/56—V. L.E. 20/70.

area are rare because there usually are posterior synechias which prevent forward displacement of the iris. Also, in those with central perforations, the anterior chamber promptly reforms upon grafting.

Anterior chamber hemorrhages are uncommon in spite of the vascularity of the cornea and congestion of the iris.

Discussion

Although the number of cases presented here is small and the follow-up in some cases short, there is evidence that this form of therapy for such ulcers is very satisfactory. The fact that eyes so seriously affected were even saved is of importance. The postoperative care in such cases is tedious, fraught with complications, and vexing to the patient and surgeon. Even so it is desirable to pursue a vigorous treatment course in these cases, and it is certain that many eyes can be saved.

This method of treatment seems superior to penetrating keratoplasties and application of conjunctival flaps because the resultant scarring is less and a good bed is provided for future penetrating keratoplasty. Also, in recurrent ulcers, the operation seems to prevent relapses. So far we have not seen a recurrence of a dendritic ulcer *in a graft* (longest follow-up in penetrating and lamellar keratoplasties, six years). One of our cases had a recurrence in the cornea at the edge of the graft which spread onto the graft itself, but this is the only example of true recurrence we have seen.

Summary and Conclusions

1. Therapeutic lamellar keratoplasty is indicated in patients with chronic superficial herpetic ulcers which have resisted treatment for two to three months.

2. It is also indicated in those with deep ulcerations which are resistant to treatment, even if the ulcer has perforated.

3. It is a valuable procedure in patients with recurrent herpetic ulceration to prevent recurrences.

4. The technique of performance of lamellar keratoplasty in such cases is described.

5. Some of the complications and their management are discussed.

6. The results in the treatment of nine cases are described. Three cases had perforations, yet underwent successful keratoplasty. One case developed a Monilia infection of the edge of the graft, with complete clouding, three months after surgery, due to prolonged antibiotic therapy. One case developed a wound separation six weeks after surgery, with clouding, but healing eventually occurred. Four cases had uneventful postoperative courses, and developed fairly good vision after eventual healing.

University of California Medical Center (22).

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1. Sanders, T. E., and Ley, A. B.: Communication to A.M.A. Sec. Ophth., June, 1956.
2. Hogan, M. J.: Corneal transplantation in the treatment of herpetic disease of the cornea. Am. J. Ophth., **43**:147-160 (Apr., Pt. II) 1957.

THE THERMAL EFFECT ON OCULAR TISSUES*

Of surgical diathermy currents with frequencies used in treatment of detached retina

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The basic electrical and thermal phenomena of electrocautery of the eye have been under investigation in the Division of Ophthalmology and Department of Biophysics at the University of California at Los Angeles for the past three years. The senior author initiated the study as a background for improvement in the type of cautery used in retinopexy and cyclodiathermy, suspecting that many untoward postoperative complications are results of injudicious use of diathermy current on the eye. Some of these results might be: new holes and breaks in the treatment area and remote areas; retinal hemorrhage at some distance from the area treated; massive detachment of the vitreous with consequent pulling of the retina toward the vitreous base; shrinkage and fixed folds of the retina; subretinal transudate; separation of the choroid; necrosis of the sclera; and unusual inflammatory reactions.

To date, the studies by Henry Knoll include the following, which are, or will be, reported elsewhere:

1. Determination of the output characteristics of the Walker diathermy unit.

2. Determination of the electrode impedance characteristics in saline-agar preparations and of eye tissue impedances upon surface treatment with current frequencies between 100 cycles and 10 megacycles.

3. Determination of the spread of heat in saline-agar preparations, with egg albumin as the visual indicator.

4. Measurement of increases in intraocular pressure caused by scleral shrinkage, and the time variant of these changes.

5. Determination of the shrinkage temperature of cornea and sclera,[1] and also of the vitreous.[2]

For this presentation, one aspect of these studies is reported: namely, the rise in temperature of eye tissues treated with high frequency currents, frequencies being such as might be encountered in retinopexy. In the pilot experiments the temperature rise in the sclera, measured by use of a thermocouple, varied from 2°C. to 16°C. when the electrode was applied for three seconds, three mm. from the thermocouple. It seemed worth while to analyze the reasons for the variations in results by relating them to simultaneous measurements of voltage, amperage, and temperature rise, upon treatment of different areas of the sclera, with variations in application of the electrode from point surface, to partially penetrating and perforating, and rapidly repetitive semiperforating, in order to simulate actual conditions of treatment at surgery.

The same experiments were then repeated on the cornea, where the tissue is homogeneous and the effects of blood flow eliminated. It is realized, of course, that the amperage registered on the ammeter, connected with the active lead from the generator, is not a

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measure of the actual amperage flowing through the tissue, but does represent current delivered to the electrode.

Experiments

Cats were the experimental animals. Nembutal anesthesia was used with supplementary local two-percent Xylocaine and adrenalin as needed. After a large canthotomy and rongeuring away of the lateral wall of the orbit, the sclera was exposed. The external rectus and inferior oblique muscles were tenotomized, better to mobilize the eye. Traction sutures were placed in the conjunctiva and muscles, as needed, to hold the eye in position. The cat's sclera, in a band encompassing the ciliary region, between the limbus and the insertion of the rectus muscles, is quite thick. Contrariwise, it is extremely thin behind this region (fig. 3). A small incision, parallel to the limbus, was made through the sclera, over the ciliary body, so that the thermocouple could be located between sclera and ciliary body. This parallel incision avoided the large vessels that encircle this region circumferentially, both in episclera and subsclera. Uncontrollable bleeding occurred if radial scleral incisions were made.

Behind the ciliary body, the cat's sclera is so thin as to be comparable to the fine posterior scleral fibers, lamina fusca, lying just anterior to the choroid in the human, after the outer sclera has been dissected away. The electrode size, time of application, and distance of the site of application from the thermocouple, in each series of experiments, are stated in the table in which the data are presented. It must be remembered that the heat is inversely proportional to the square of the distance from the thermocouple. This means that the thermocouple could be recording a rise in temperature of 3°C. or 4°C. at three or four mm. from the thermocouple, whereas the temperature at the electrode tip could be 60°C., the shrinkage temperature for collagen.[2] The various types of diathermy applications were made posterior to the thermocouple, in a semicircle, equidistant from the thermocouple tip, and then repeated anterior to the thermocouple, in the thicker, more vascular sclera.

Following a series of single, point surface, and partially penetrating treatments, five rapidly successive treatments were given to determine the accumulative effect. These were followed by one or two single perforating treatments. The currents used were: 60-cycle, 6,000-cycle, 1.5-megacycle, 10-megacycle, and Walker spark-gap unit with dial set at 30 and at 40.

The same sequence of electrode applications was repeated on the cornea. A small corneal-lamellar section was made for insertion of the thermocouple into the stroma of the cornea. Perforation was the final procedure.

For recording temperature, an iron-constantan thermocouple was used in conjunction with a Leeds and Northrup continuous balancing bridge strip recorder. An ice bath was used for the reference junction.

Other equipment used was as follows: a Walker Combination Diathermy Unit to generate the damped oscillations; a Hewlett-Packard test oscillator in conjunction with an audioamplifier to generate the 6,000-cycle current; an Army Signal Corps BC-191 transmitter to generate the 1.5- and 10-megacycle current; house current, regulated by means of a Variac, as the 60-cycle source. A General Radio vacuum tube voltmeter was used to measure the voltage, and thermocouple ammeters were used to indicate the currents.

Results

Once the voltage needed from each generator to give effects similar to those seen at surgery was estimated by preliminary trial, it was found that the temperature rises could be kept reasonably consistent from one frequency to another with sustained, undamped waves, and with damped waves from the spark-gap machine, providing the time and site of the electrode application, size of elec-

TABLE 1

COMPARISON OF RISE IN TEMPERATURE WITH 10-MEGACYCLE

(Oscillator and with Walker unit: two-mm. electrode: partially penetrating: 46 seconds: five-mm. from thermocouple.)

	Walker	10 mc.
	°C.	°C.
Sclera:	6	7
	6	5
	2	9
	4	4
	1	6
	7	
	6	
	6	
	6	
	6	
	8	
	7	
Cornea:	6	6
		3
Average:	5.5°C.	5.7°C.

TABLE 2

CONSECUTIVE EXPERIMENTS ON SAME EYE

(Walker unit and 10-mc. oscillator:sclera two-mm. electrode: partially penetrating: 46 seconds)

Unit	Volts	M-amps	mm. from TC	°C. rise
10 mc.	38	88	5	7
Walker		30	5	6
Walker		30	5	6
10 mc.	40	76	5	5
10 mc.	41	74	3	9
Walker		25	3	13
Walker		30	3	12
10 mc.	42	66	3	4

trode, and nature of electrode contact were the same (tables 1, 2, and 3 and records 1 and 5).

Consistent and significant differences in temperature rise were recorded if different areas on the sclera were treated. For instance, when the posterior sclera was treated briefly for three to five seconds, and this area became readily dried on exposure, the temperature rises were small. When the anterior, more vascular, sclera was so treated, the temperature rises were definitely greater (table 4 and records 2 and 3).

It was difficult to duplicate exactly the electrode contact, as this contact was made by hand and not with micromanipulator. It was apparent that increased pressure on the electrode, increasing the contact, increased the temperature rise substantially.

It was also noted that, if the electrode was applied to a previously treated and charred area, very low amperage was recorded and minimal heat was generated in the tissue. If this area was perforated by the electrode, producing better contact of electrode, bringing the electrode point into blood or lymph, marked rise in temperature again occurred, regardless of the frequency or wave form (record 4).

As long as only the point of the electrode touched the tissue, thermal effects were consistent, but, as soon as the point was buried in tissue, or the uninsulated base of the electrode was in contact with the tissue, giving more surface effect, the temperature rise was

TABLE 3

CONSECUTIVE EXPERIMENTS ON SAME EYE: TIME TAKEN TO GET 10°C. RISE IN TEMPERATURE

(Walker unit set at 45 and 10-mc. oscillator: cornea two-mm. electrode: partially penetrating: five-mm. from thermocouple)

Unit	Volts	m-amps	Sec.	°C.	Appearance
Walker		32	30	10	3 mm. sunburst
Walker		32	15	9	3 mm. sunburst
10 mc.	50	88	22	10	1 mm. sharply outlined
10 mc.	50	85	17	10	1 m.m sharply outlined
Walker		25	27	10	3 mm. sunburst
10 mc.	38	62	40	8	1 mm. discrete
Average: Walker, 24 seconds					
10 mc., 26 seconds					

TABLE 4

HEATING EFFECT (AVERAGE) WITH DIFFERENT FREQUENCIES

0.5-mm. electrode	3 sec.	3 mm. from tc		
Frequency	*6,000 C.*	*1.5 mc.*	*10 mc.*	*Walker*
Volts	48	50	23	
Milliamperes	8	10	42	
Rise in temperature	°C.	°C.	°C.	°C.
Cornea	2.2 (10)	2.4 (11)	2.7 (13)	2
Posterior sclera	2.5 (9)	2.0 (9)	1.5 (9)	4
Anterior sclera	6.2 (3)	8.3 (3)	9.0 (3)	
Posterior sclera—5 times	3.5	10.0	2.0	
Anterior Sclera—5 times	8.5	17.5*	12.0	

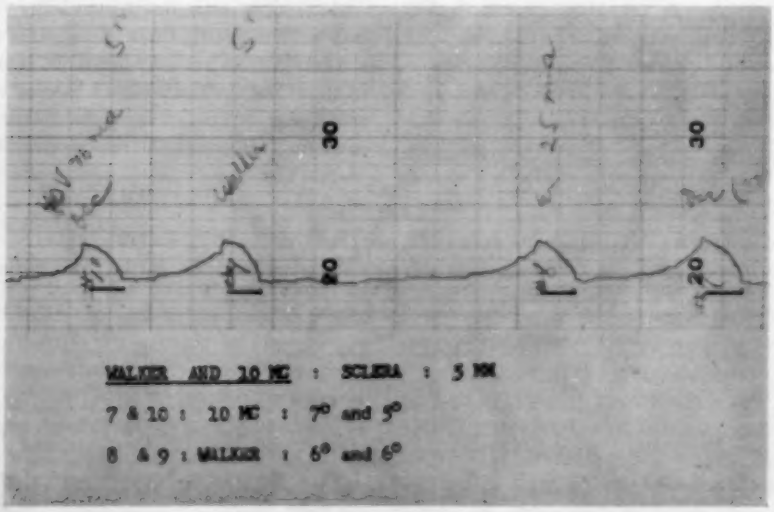
* Perforation.
( ) Indicates number of experiments averaged.

correspondingly greater and somewhat more variable. More consistent and reproducible results were obtained when the cornea was used for treatment. Here the indentation of the cornea by the electrode could be estimated by the dimpling of the cornea; conditions of semiperforation and perforation were readily ascertained by observation of leaking of aqueous or bubble formation in the aqueous (table 3).

The results show that the degree of contact of electrode with tissue is most important, and that, as long as power was comparable, frequencies of 6,000 cycles, 1.5 mc., 10 mc., or damped waves from spark-gap made little difference in the temperature of the tissue three to five mm. from the thermocouple.

Once perforation has occurred, the electrical circuit must be envisioned as being entirely different, for current then flows through fluid, amperage suddenly increases, and the temperature rise is correspondingly greatly increased, regardless of the frequency or type of waves (tables 5 and 6 and records 4, 6, and 7).

This might be expected since the heat produced is proportional to the square of the current. In fact, it would appear that the electrical circuit varies for different treatment modes and even during the duration of a given treatment. A brief (approximately 0.5



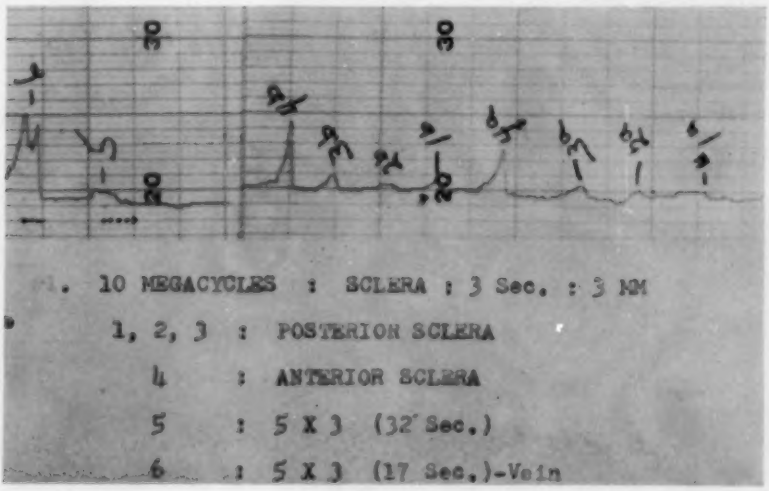
Record 1

TABLE 5

RISE IN TEMPERATURE UPON PERFORATION: COMPARED WITH NONPERFORATING APPLICATION, OTHER CONDITIONS BEING EQUIVALENT

Generator	Area	Seconds	Mm. from TC	Non-perforating °C. Rise	Perforating °C. Rise
Spark-gap	Posterior sclera	46	5	6	14
		46	5	6	31
		46	5	6	34
		46	4*	7*	28*
	Anterior sclera	46	5	6	17
	Cornea	50	4	10	12
		30	3	10	36
		30	3	10	45
		12	3	9	34
60 cycle	Cornea	3	5	2	12
6,000 Cycle	Cornea	6	3	2	10
		3	3	2	20
		3	3	2	100
		3	3	2	100
1.5 mc.	Posterior sclera	3	3	2	15
	Anterior sclera	3×5	3	11	18
	Cornea	3	4	3	13
		8	3	3	27
		3	3	3	9
		3	3	3	16
		3	3	3	19
		3	3	2	15
10 mc.	posterior sclera	46	3*	3*	17
	Cornea	6	5	6	18
		7	5	6	13
		3	3	2	14
		3	3	5	58
Electric cautery	Cornea	7	5	4	2

* TC in vitreous.



Record 2

TABLE 6

THERMOCOUPLE IN VITREOUS

(Walker unit and 10-mc. oscillator: sclera: 46 seconds: two-mm. electrode: four-mm. from TC)

Unit	Volts	M-amps.	°C. Rise
10 mc.	42	70	3
Walker		25	7 spread along vessels
Walker		38	28 perforated
10 mc.	41	79	17 perforated

second) surge in current is noted in almost every application. The value of the current during this surge is one and one-half to four times the value through the remainder of the treatment time. The highest ratio of initial surge to steady values were at the lowest frequency. During perforation, another surge is noted at the instant of perforation. Here the current value may be 50 to 100 times the value prior to perforation. These changes may be explained as follows: the early surge represents a flow of current through the extracellular fluid. The heat developed vaporizes fluid and impedance rises, for the electrode is now in contact with cell membranes.

Upon perforation, when the needle has passed through the cellular tissue, the impedance drops dramatically, for two reasons: (1) because of increased contact of electrode tip with tissue and tissue fluids; and (2) because of contact, or immersion, in aqueous or vitreous where impedance is appreciably lower. The same effect is seen when a blood vessel is perforated during point surface treatment.

PRESENT CONCEPTS OF FULGURATING, COAGULATING, AND CUTTING CURRENTS AS RELATED TO THESE EXPERIMENTS

When direct current passes through tissue, the amount of heat produced is proportional to the resistance of the tissue, the time the current flows, and the square of the current density.

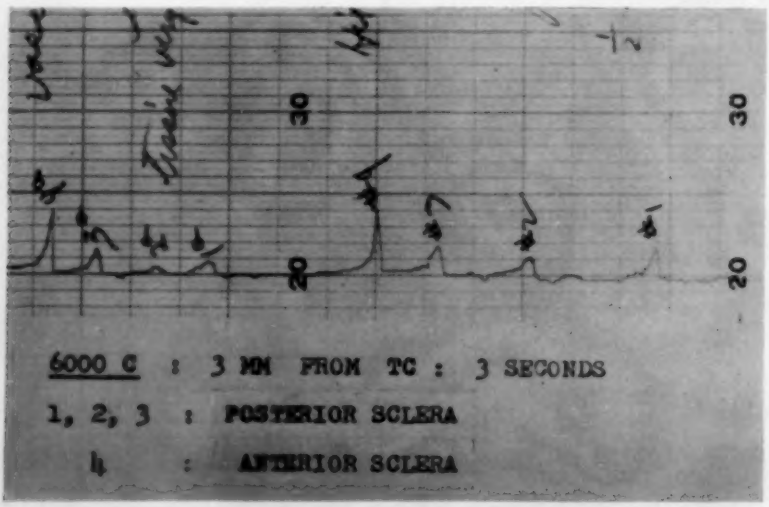
I—Amperes
V—Volts
R—Resistance in ohms
T—time in seconds

$$\text{Current: } I = \frac{V}{R} \quad \text{(Ohm's Law)}$$

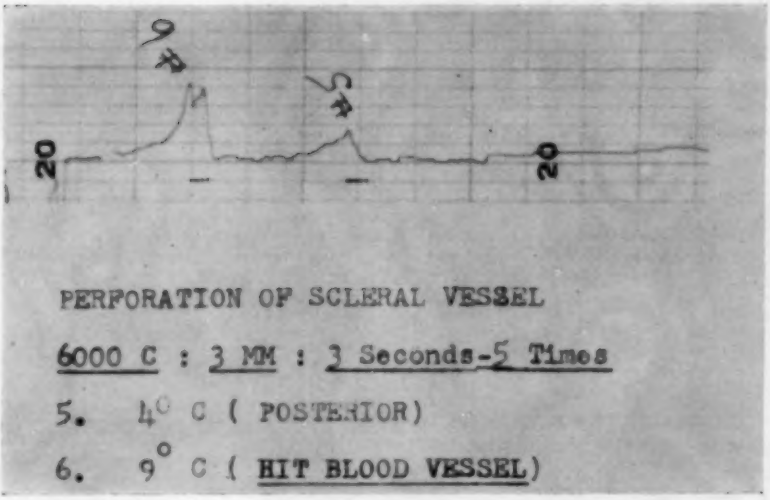
$$\text{Power: Current times voltage} = I^2R = \frac{V^2}{R} = \text{watts per second}$$

$$\text{Heat: Calories} = 0.24\ I^2RT \quad \text{(Joule's Law)}$$

With alternating current, the calculations are complicated by the fact that voltage and

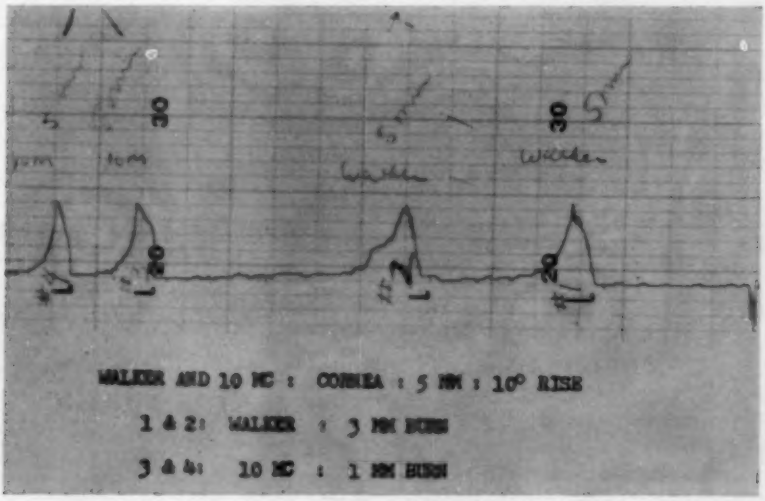


Record 3



Record 4

amperage are now oscillating and the effective current passing through the tissue must now be calculated as depending upon the maximum rise and fall with each cycle. This effective current value is computed as a trigonometric function of maximum current strength and frequency of oscillations in terms of its equivalent in direct current, and found to be 0.707 times the maximum value[3] (diagram 1). Then, too, in consideration of alternating current we must consider the inductance and capacitance which tend to oppose current flow. The effects of these, together with resistance, are known as impedance. Inductive and capacitive reactance, opposing change in current flow, unlike resistance, are not associated with production of heat. They are dependent upon frequency,



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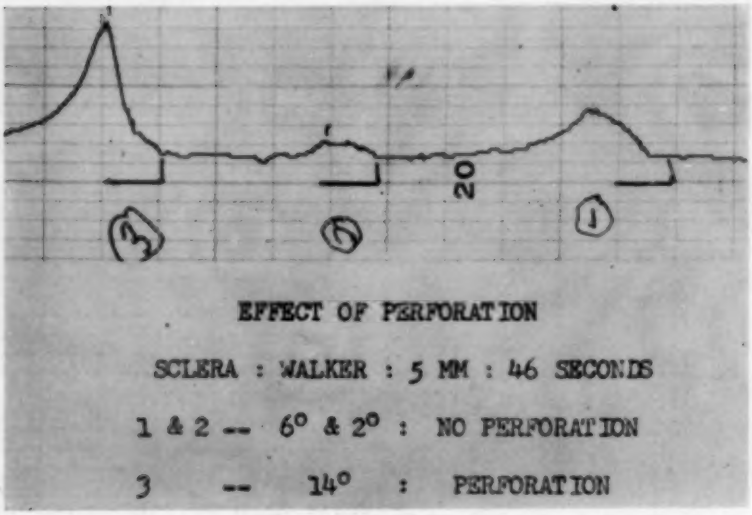
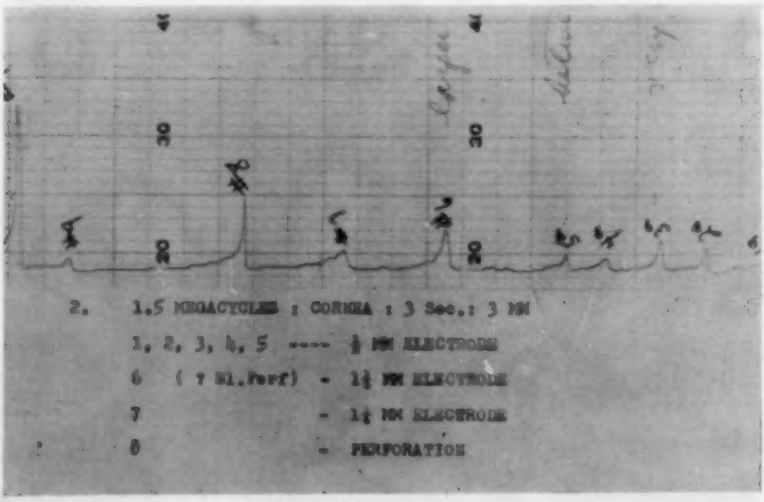


Record 6

the value of inductance, and the value of capacity.

The inductive reactance X_L, expressed in ohms, is proportional to the inductance and the frequency F. That is: $X_L = 2\pi L F$. The capacitive reactance, X_C, is inversely proportional to frequency and capacitance. That is: $X_C = 1/2\pi F C$. It is seen then, that the higher the frequency, the greater the inductive and the smaller the capacitive reactance.

From these equations, we see that, with resistance and capacity connected in parallel, an increase in capacitance and an increase in frequency, in a circuit, could result in a capacitive reactance so very small that most of the current would flow through the circuit of



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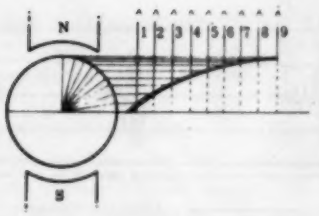


$$I_{EFF} = \frac{\text{EFFective Value (RMS)}}{\sqrt{\text{Average of the Sum of the Squares of } I_{ins}}}$$

$$I_{EFF} = 0.707 \times I_{max} \qquad I_{max} = 1.414 \times I_{EFF}$$

Diagram 1 (Irvine and Knoll). Effective value of a sine wave.

the condenser, and, as a result, relatively little heat would be produced for the amount of current flowing through the cricuit[4] (diagram 2).

In the body, cell membranes presumably act as condensers, having capacity, and the extracellular and intracellular fluids act as resistance. The condensers offer but little impedance to the passage of currents of high frequency, and so, at high frequency, large amounts of current can flow through the body with little relative heating effect. The heating is principally due to the resistance offered by body solutions to flow of current, and, once the impedance of the tissue has decreased until the resistance of the condenser (reactance) has become small in comparison with the resistance of the fluids, much of the current will be shunted through the cell-membrane, condenser route[5] (diagram 3).

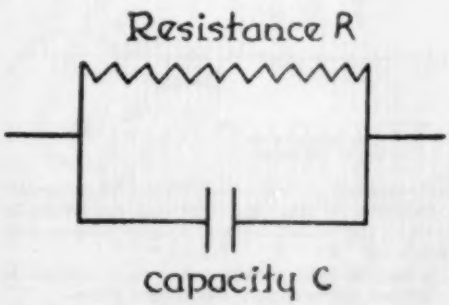


Diagram 2 (Irvine and Knoll). Characteristic impedance circuit.

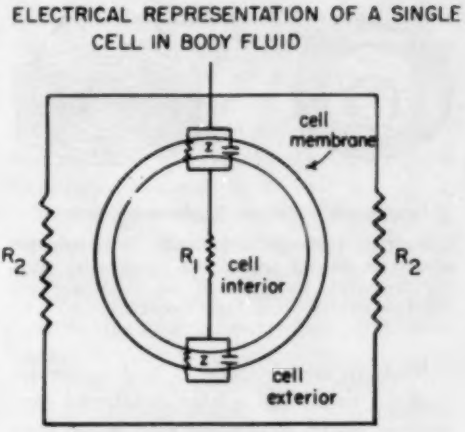
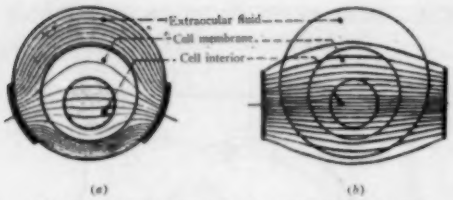


Diagram 3 (Irvine and Knoll). Body fluids are primarily resistive in nature, whereas cell membranes may be represented as "leaky" condensers.

This concept explains why, in tissues with a high cell density, the current at low frequency, taking the path of least electrical resistance, will spread laterally; whereas at high frequency, the current will pass through intracellular and extracellular fluids as well, and will have less tendency to flow laterally[6] (diagram 4, table 3).

When current of high density is concentrated on a small electrode, the current entering the tissue immediately beneath the electrode will be very dense, rapidly decreasing in intensity in surrounding tissues. Heat is then generated at the site of the electrode.

If the electrode is held away from contact with the tissue, the body acts as the indifferent electrode, and, if voltage is sufficiently high, a spark will jump from electrode tip to tissue. The heat of this spark will depend upon the amperage which, in turn, depends on the distance of tissue from the electrode tip. The airspace is ionized and, if current is maintained, the tissue can be desiccated by the spark. This is called fulguration. The heat is slight and the area affected is superficial.



(a) Classical diathermy; *(b)* short-wave diathermy

Diagram 4 (Irvine and Knoll). Representation of current flowing around cell (resistance) when low frequency, and through cell membrane and cell (condenser) when high frequency.

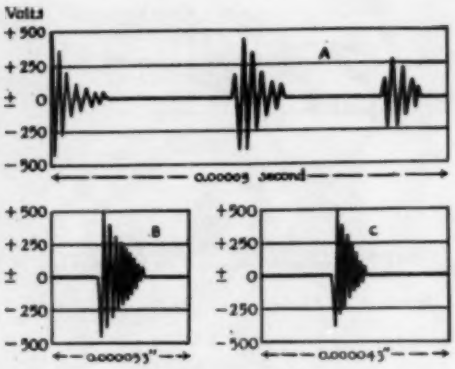


Diagram 5 (Irvine and Knoll). Types of damped diathermy currents.

Now, if the electrode is held in contact with the tissue and a large indifferent electrode is placed somewhere else on the body (this may not be necessary—the body again acting as indifferent electrode), high frequency current will pass from the small active electrode through the body to the indifferent electrode, and, as a result of increased density of current at the active electrode, the tissue will be heated and coagulated for some distance below and surrounding this electrode, depending upon the strength of current, resistance of tissue, and time of flow of current. If the tissue is heated slowly enough to allow some spread of heat and coagulation of tissue proteins without vaporization, this heating effect is called electrocoagulation. The spark from the electrode is relatively large, broad, irregular, and diffuse. It can be visualized if the electrode is held a bit away from the tissue.

The current to produce coagulation is readily generated by a spark-gap generator producing current in unsustained, damped waves. Here the peak amplitude of voltage and current diminishes to zero value, with the next train of damped waves following after a period of no current flow[7] (diagram 5). These wave trains may recur at any rate. In the Walker Unit, they recur at a rate of approximately 6,000 pulsations per second (diagram 6). The tissue is heated more slowly, with time for spread of heat, and consequently the final effect is coagulation of tissue for some distance beyond the electrode. Damped pulsations allow more time for spread of heat simply because the amount of current per unit time is less than with undamped current of similar peak voltage and amperage. We must remember that the pointed electrode presents more resistance to flow of current than would a blunt

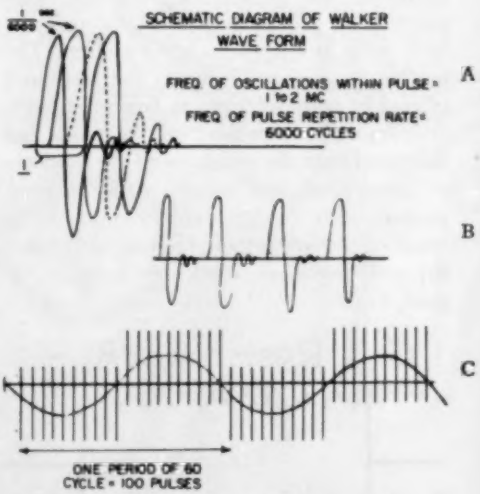


Diagram 6 (Irvine and Knoll). (A) Schematic appearance of spark-gap generated oscillations as seen on the oscilloscope with a sweep frequency of 60 cycles.

(B) The envelope for each cycle is believed to represent approximately 100 damped pulses.

(C) These may be seen, but only with difficulty at a sweep frequency of one to two megacycles.

electrode, and, consequently, the flow of current into tissue is greater with the larger electrode, if voltage is constant. The area affected then is larger.

Once tissue fluid reaches a boiling point, it will vaporize. The small electrode produces a smaller volume of vaporization. The steam produced then insulates the electrode, as steam is a good insulator and tends to confine the effect.

Now, if, on the other hand, a generator produces sustained oscillations of equal amplitude (undamped) as accomplished by vacuum tubes, or relatively well with a series of spark gaps, it is much easier to maintain a sustained current of a given effective value than when we have a train of damped waves[4] (diagram 7). The resultant spark leaving the electrode is much finer and hotter for the same peak amperage and voltage and immediately explodes the cells and vaporizes underlying cell fluid. If the needle is moved along, a fine section can be made through the tissue. This current is consequently called a "cutting" current.

With this "cutting" current, because the tissue is heated more rapidly, the spread of heat before vaporization occurs is less. If the needle were left in place, the area affected would be less extensive than with coagulating current because the immediate tissue fluid is vaporized more rapidly, the steam insulates the electrode and inhibits the spread of heat to surrounding tissues. The heat produced is still related to resistance and intensity of current, and time of current flow, whatever the frequency or wave form.

With higher frequencies, differences in impedance of various tissues diminish, and more current can pass through the body by the capacitance route, with relatively little increase in general body heat, but with marked increase in density of current at the site of the active electrode and greater production of local heating at this immediate site.

There is, however, no magical difference between damped and undamped currents in the effects they can produce. It is simply easier to generate more effective current per unit time if undamped. The flow of effective current, in terms of the equivalent in direct current, is greater for the same peak amperage and voltage[7] (diagram 8). Theoretically, use of a generator producing "cutting" current could give better concentration and localization of effect.

Swan[5, 9] has beautifully demonstrated the difference between "cutting" and "coagulating" currents on scleral cauterization. As he

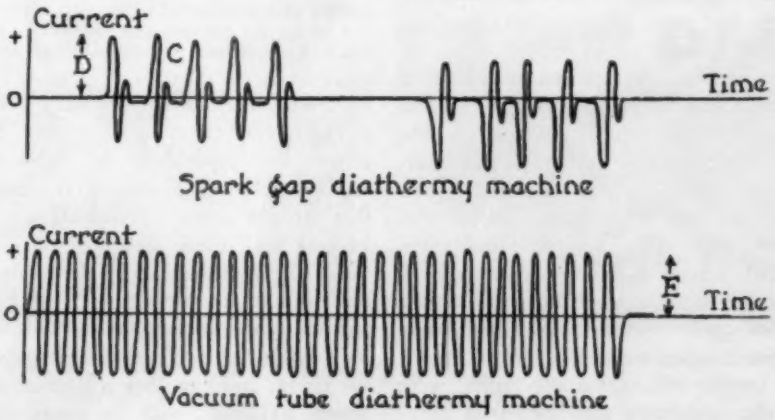


Diagram 7 (Irvine and Knoll). Representation of damped wave forms and sustained undamped wave forms.

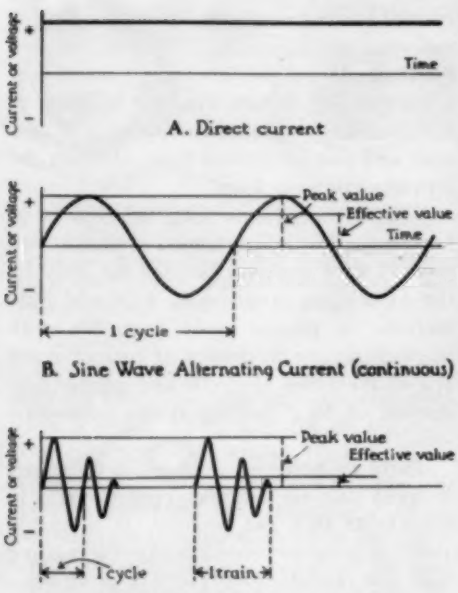


Diagram 8 (Irvine and Knoll). Illustrating larger surface effect on cornea or sclera with Walker Unit than with 10 megacycle current, but relatively equal effects on retina. Spread of current effect with the lower frequencies of the Walker Unit is greater, but the cooling gradient is steeper so that the end effects deep to the electrode are indistinguishable.

says, both types of current are useful; cutting for focused local effects; and coagulating for shrinkage and more diffuse effects, particularly if the eye is soft.

In the experiments reported here, heating effects were not significantly different, from one frequency to another, as long as the power delivered to the electrode was approximately the same (table 4). Theoretically, coagulating current should be less dense and the effects more diffuse. As seen in Figures 1 and 2, the effects on the cornea were spread over a larger area, when spark-gap, 60-cycle, and 6,000-cycle current were used, than when frequencies were 1.5 and 10 megacycles. Deeper effects, on the retina, were hardly distinguishable with the various frequencies (figs. 1, 2, 3, and 4; diagram 9).

Currents of different frequencies, although measuring the same amperage at the

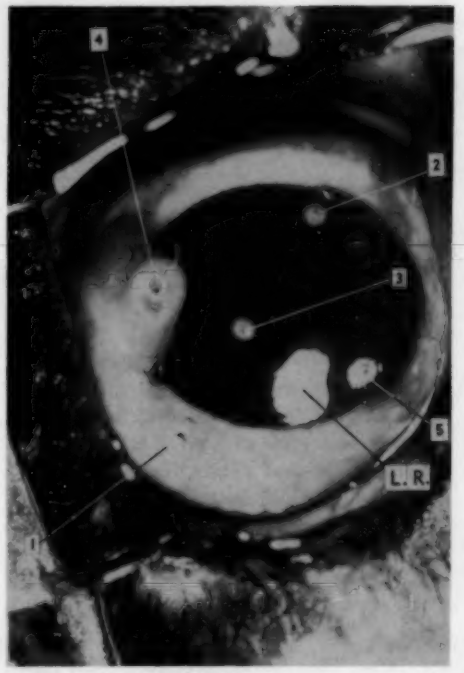


Fig. 1 (Irvine and Knoll). Cornea: Electrode applied for seven seconds.

1. 6,000 cycles: 50 volts; less than 10 milliamperes; slight perforation.
2. 1.5 megacycles: 50 volts; 10 milliamperes; no perforation.
3. 10 megacycles: 48 volts; 100 milliamperes; no perforation.
4. Walker unit: 100 milliamperes; perforation—bubbles and steam.
5. 60 cycles: eye very soft.

L.R. Light reflex.

electrode, will, of course, vary greatly in strength and effect as they flow through tissue, the percentage of current flowing through heat-producing resistance and that through nonheat-producing capacitance varying with tissue structure and composition. Effective heating by the various currents cannot be estimated on a basis of voltage and amperage measurements alone, and it is difficult to interpret the complexities of the circuit and how they will affect the final result. Evidently, with the range of power and the standardization of application of current in our experiments, variation in frequency was less basic in determining the final

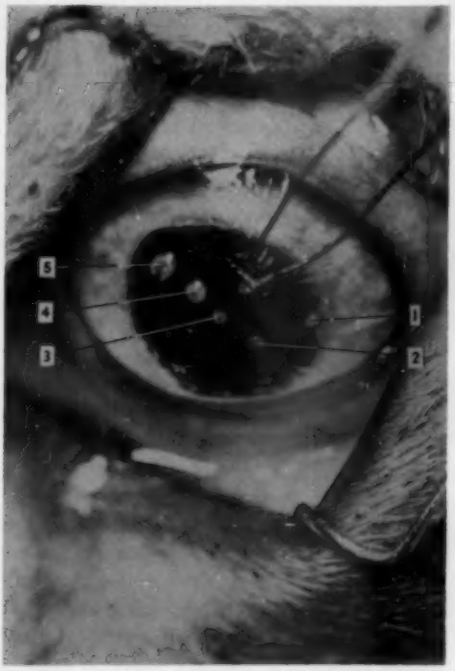


Fig. 2 (Irvine and Knoll). Cornea: Electrode applied 3.5 seconds; 3.5 millimeters from thermocouple.

1. 10 megacycles: 50 volts; 130 milliamperes; temperature rise, 2°C.
2. 1.5 megacycles: 50 volts; 10 milliamperes; temperature rise, 1°C.
3. 6,000 cycles: 50 volts; 2 milliamperes; temperature rise, 2°C.
4. 6,000 cycles: 50 volts; 70 milliamperes; slight perforation; TC came out.
5. Walker unit: Temperature rise, 2°C.

burn than were other conditions.

For example, once the eye is perforated and the electrode tip immersed in body fluid (aqueous, vitreous, or blood), the entire electrical circuit is altered. There is sudden marked drop in impedance with coincident surge of current and consequent increased production of heat, regardless of the frequency of current used.

Practical implications of these observations

The current and consequent heating effect will vary from one application of the electrode to another, depending upon the area of

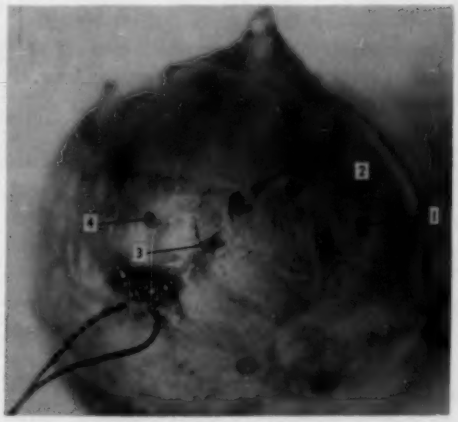


Fig. 3 (Irvine and Knoll). Sclera: 0.5-mm. electrode.

1. 1.5 megacycles: 3.5 seconds; 50 volts; 12 milliamperes.
2. 10 megacycles: 4.5 seconds; 40 volts; 100 milliamperes.
3. 6,000 cycles: 4.0 seconds; 50 volts; (40) 5.0 milliamperes.
4. Walker Unit: 3.0 seconds; 22 milliamperes.

contact, the inherent extracellular and intracellular fluid content, the blood flow, and the electrical resistance of the tissue treated as it is affected by abnormal drying and charring.

From the studies here reported, it seems that clinical evaluation of the burn produced, as judged by direct observation of the sclera and the retina at the time of treatment, is as

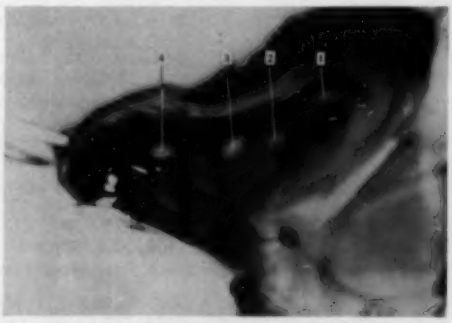


Fig. 4 (Irvine and Knoll). Retina: 0.5-mm. electrode; effects on the retina of the treatment of the sclera, shown in Figure 3.

1. 1.5 megacycles.
2. 10 megacycles.
3. 6,000 cycles.
4. Walker spark-gap unit.

practical an indication of the current that should be used as any measurements of voltage, amperage, or heat produced, as long as perforation of the globe does not occur.

Upon perforation of the cornea by the electrode, temperature rises up to 100°C. were produced in the aqueous with currents comparable to those usable in retinopexy, regardless of the frequency of the current. One might assume then that similar temperature rises could be produced in the subretinal fluid if the electrode perforates into this fluid.

Although shrinkage of the vitreous was not observed in these experiments, it is entirely possible, when the electrode perforates and contacts the vitreous, that sufficient heat is generated to cause contraction of the collagen fibers of the vitreous. Brunish demonstrated the shrinkage temperature of these fibers to be 60°C.[2]

It is very possible that subretinal fluid, with its high protein content, could be heated to a temperature at which the adjacent retina would be made edematous and possibly foreshortened. This diffuse effect might not be apparent at the time of surgery, but postoperatively the retina would appear edematous.

To avoid damage by diathermy, the surgeon must know his own machine and must have clinical experience judging the reaction on sclera and retina, always starting treatment with the production of too little effect, increasing to the desired effect. These precautions must be observed even when conditions appear to be more controlled by having done lamellar resection and treating the choroid and suprachoroid under direct observation. The surface effect on the scleral fibers overlying the choroid can appear misleadingly small compared to what one is accustomed to seeing when treating the intact more hydrated sclera where burn effects are more readily visualized. Any treatment must be constantly controlled by observation of the retina.

The ideal apparatus for surgery of detached retina should be constructed to deliver galvanic current and both sustained and damped-wave high-frequency current. This would facilitate production of chemical, fulgurating, coagulating, and cutting effects, all of which have a place in surgery of detached retina. Ideally, the machine would so control current as to prevent large surges when sudden drop in electrical resistance is encountered, as occurs when the electrode perforates the globe.

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VISUAL ACUITY TESTS FOR NEAR: IMPLICATIONS AND CORRELATIONS*

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Near vision has been studied from many aspects. Galton,[1] in 1885, tested the farthest distance at which four-point type could be read in 7,000 persons, from six to 81 years of age. He concluded that the near visual acuity improved rapidly from childhood to a maximum at the age of 20 years, then declined very gradually till the age of 45 years, and more rapidly thereafter. Chapanis,[2] in 1950, checked the visual acuity of 574 persons from seven to 77 years of age with a reduced Snellen chart at 32 inches and likewise found a curvilinear trend with the highest score in the 15 to 20-year-old group.

In subjects corrected for errors of refraction and accommodation a close correspondence exists between the visual acuity at 20 feet and that at reading distance (Bjerke,[3] Landolt,[4] Snell[5]) with these exceptions (Kestenbaum and Sturman[6]): Near vision may be better than that for distance in those with peripheral opacities of cornea or lens, irregular astigmatism, or pendular nystagmus—because of pupillary constriction or convergence, respectively. Near vision is usually poorer than far vision in the presence of a central opacity of the cornea or lens, or of an incomplete central scotoma.

DISTANCE ACUITY VERSUS NEAR ACUITY IN CORRECTED EYES

Though an adequate optical correction in otherwise normal eyes renders the measurements of far and near visual acuity parallel, the two measurements are not as identical as has been sometimes assumed. Several investigators have demonstrated a definite progressive diminution of acuity as the distance decreases below one meter. Musylev[7] noted an eight-percent difference between the threshold acuities at 100 cm. and 35 cm. Giese[8] found that 400 subjects with a mean acuity equivalent to 20/12 at 100 cm. averaged only 20/15 at 40 cm. and 20/22 at 20 cm. Since the accommodative difference between 100 cm. and 35 cm. accounts for only three-percent diminution, other factors must be involved. Freeman[9] evoked the phenomenon with fixed artificial pupils, in both light and dark adaptation, and with precautions to avoid psychologic awareness of either the distance or magnitude of the stimulus. The conclusion, reached by Luckiesh and Moss,[10] that accommodation and fixation are steadier and adjusted more precisely for distance than for near is generally accepted. Individuals with a corrected acuity of just 20/20 cannot read words in small lower case letters that subtend the same visual angle, which at 14 inches is three-point type, though four-point type (visual angle 1.25) is read then without difficulty.

DISTANCE ACUITY VERSUS NEAR ACUITY IN UNCORRECTED EYES

In persons with uncorrected errors of refraction the acuity at 20 feet does not correlate highly with that at reading distance. In a perfect correlation the coefficient is 1.00; in no correlation, the coefficient is zero; that between far and near Snellen scores is 0.56 (Sulzman, Cook, and Bartlett[11]). Since the far test does not predict near-point ability, tests at the near distance should prove no less valuable in the school than in industry.

Kephart[12] established that unsatisfactory near acuity is quite as common in school children as in young adults. The Ortho-Rater test for binocular acuity at 13 inches, given to 2,181 pupils in grades three to 12, showed an S-curve of visual performance that was almost identical with that previously found

* From The Department of Ophthalmology, Northwestern University Medical School.

in 7,655 industrial employees. A comparison of the binocular acuities of these children for far and near gave a correlation coefficient of 0.55. Of the 541 children who failed the near test, 42 percent ranked above standard in the far test. A definite correlation was noted between school achievement and high near-test scores.

In a St. Louis project,[13] sponsored in part by the National Society for the Prevention of Blindness, all the current screening procedures were applied to 606 children in the first grade and 609 children in the sixth grade. The validity of the various screening judgments was checked by ophthalmologic examination, according to which 31 percent needed attention. A high standard Snellen far test (20/20) combined with a high standard near test (20/20 equivalent in reduced Snellen optotypes) secured the same number of correct referrals as the Massachusetts Vision Test. Actually the trained technician referred fewer students incorrectly with this combination than with the Massachusetts Vision Test, though the school nurse had the reverse experience. The high standard near test alone referred correctly almost as many students as the high standard Snellen but resulted in more incorrect referrals. The different examiners obtained similar findings with all the screening methods on sixth grade students, but with first-graders the results of the school nurse and of the trained technician with the screening machines and near-vision test were much less consistent.

Near-vision tests

The Snellen test for distance is endowed with recognized standards of test character and recording that have not been attained as yet in the near-vision test. Some maintain that the only accurate means of measuring the acuity of near vision is with reduced Snellen optotypes. Others hold that the near test should have a practical relation to reading experience. The suggested pitfalls of context and word configuration can be avoided by using unconnected words composed wholly of small lower-case letters such as: room, ocean, cannon, arrow, saucer (Lebensohn[14]). Letters equal in width and height, as in the Snellen optotype, are both the most suitable and the most legible (Roethlein[15]). Though the point system refers to the size of the type body, a standardized type can be selected, such as Century School-book, where the small sorts are just half the point size. For a high standard near-vision test at 14 inches, four-point type is suitable. The small lower-case letters are then two-point or 0.7 mm. in height.

The Guibor near-vision test[16] shows a gradation of suitably reduced E symbols in different positions. Only one symbol is exposed at a time so that pointing is avoided. A typical case cited by Guibor was that of a 13-year-old boy with six diopters of hyperopia in each eye. Unaided, his vision at 20 feet was: R.E., 20/13; L.E., 20/13; but his near acuity was only equivalent to R.E., 20/65; L.E., 20/50. With young children the near E test does not match the reliability of the E chart for distance. Because of the restricted area of stimulation, concentration on only one small symbol creates rapid retinal fatigue. Perhaps the E in any one position should be in sets of four or five like a word; or the E-s in a set could be varied and those in a certain position counted.

Compact commercial machines have been developed to check sundry visual functions, including far and near acuity. The standard Snellen test is definitely more reliable than that secured by optical simulation of distance. Imus[17] states that for distant vision the coefficient of reliability of the standard Snellen test is 0.97; of the Ortho-Rater, 0.84; of the Sight-Screener and Telebinocular, 0.74. The visual acuity test for near is innately less accurate than that for distance —a point that Snellen emphasized; but the various near tests are fairly consistent.

For monocular near acuity, the coefficient of reliability of both reduced Snellen optotypes and words of small lower-case letters is 0.78; of the Ortho-Rater, 0.77; of the

Sight-Saver and Telebinocular, 0.71. The Telebinocular tests near vision at 16 inches; the Sight-Screener at 14 inches; and the Ortho-Rater at 13 inches. A screening machine weighs about 25 pounds, is self-contained, rigid, portable, provides a constant brightness and requires little space for operation. The objections to their introduction for routine school surveys are high cost, need of a trained technician, excessive time consumption, and too many over-referrals.

The basic method of designating near visual acuity is in fraction form with the denominator specifying the distance at which the details of letters subtend a visual angle of one minute and the numerator noting the farthest distance at which these letters can be read. The decimal notation of acuity and the visual angle in minutes are reciprocals of each other. For a chart read at 14 inches, the decimal notation of six-point type is 0.5; the visual angle is hence two, and the distance at which the details subtend one minute is 2.0 by 14 or 28 inches. If a student in a sight-saving class reads with a visual aid six-point words at four inches, his corrected near acuity is accurately noted as 4/28 (six-point). Though the idea has not caught on, it seems logical to designate acuity by the visual angle and to use the term "snellen" uncapitalized for this measurement, just as words like ohm are used in physics. Thus eight-point type could be labelled 2.5 snellen, and if read at 4 inches, the acuity would be $\frac{4}{2.5 \times 14}$ or $\frac{4}{35}$ (eight-point). For testing subnormal vision, a transilluminated near-vision chart, which is now available, solves the problem of providing adequate illumination with the chart held close to the face.

Though the customary reading distance is 14 to 16 inches, a testing distance of 10 inches, the conventional "near-point of distinct vision" may have advantages from the screening standpoint. A person who reads well at 14 inches can with effort read at 10 inches as the eyes must have at least one diopter of reserve accommodation to read comfortably.

The newest official formulation of visual efficiency[18] is marked by a radical re-evaluation of the disability incurred by poor near vision. A critical drop in visual assessment ensues in passing from six-point print, assigned a visual efficiency of 90 percent, to eight-point which is allotted now only 50 percent. The near measurements are made at 14 inches (table 1).

Visual screening versus ophthalmologic examination

Visual screening has proved invaluable as a means of securing professional attention for those who would be otherwise neglected. The Snellen letter test at 20 feet ranks as the most accurate single screening procedure; and for children over four years of age the far E chart is the most reliable variation. But both err on the side of under-referral and locate less than 60 percent of the students needing help. During the depression the Illinois Society for the Prevention of Blindness screened 1,870,000 school children with the Snellen chart over a five-year period and thus found 10 percent in need of corrective lenses.

Surveys of similar groups by ophthalmologic examination, however, indicate that 22

TABLE 1

1955 A.M.A. VISUAL EFFICIENCY TABLE

Distance Acuity at 20 Feet		Equivalent Near Acuity at 14 Inches	
Snellen	Visual Efficiency (%)	Point	Visual Efficiency (%)
20/20	100	3	100
20/25	95	4	100
20/32	90	5	95
20/40	85	6	90
20/50	75	8	50
20/64	65	9	40
20/80	60	12	20
20/100	50	14	15
20/200	20	24	5

to 25 percent would benefit by glasses. Most ophthalmologists hold that a hyperopia, significantly over 1.0D., requires correction. An ophthalmologic examination of all 188 children at the University School, Ohio State University,[19] showed that 25 percent had significant errors of refraction, and that an additional 7.4 percent had significant ocular muscle imbalances, making the total that needed eye care 32.4 percent. Practically the same findings were revealed in the ophthalmologic examination of 1,215 school children in the St. Louis project.[13] In Philadelphia, a survey of deaf school children by the Snellen chart indicated that 15 percent had defective vision. In a later survey of 960 deaf school children, in which every child was given an ophthalmologic examination, Stockwell[20] found that 45.5 percent needed glasses—a noteworthy figure, as it is twice the percentage in hearing school children.

An early effort to improve screening efficiency was introduced by T. H. Eames in his five-point Eames Eye Test,[21] copyrighted in 1938. This included (1) an abbreviated distant acuity chart, (2) a lens of +1.5D. sph. for the hyperopia test, (3) a near-vision test, and stereoscopic slides to test (4) heterophoria, and (5) fusion. A simplification of this program, the Massachusetts Vision Test, was developed by Albert Sloane in 1940. Yasuda and Green[22] found that the +1.5D. hyperopia test checked correctly in 50 percent of the nine- to 11-year-old group, and in 70 percent of older school children. They suggested that the test be changed to +2.25D. in grades 1 to 3; to +1.75D. in grades 4 to 7; and that 20/30 should be passing in ages six to eight.

Though a satisfactory reading ability may be attained in spite of refractive errors, ametropia is an aggravating factor in many cases of dyslexia. In reading failures, the incidence of hypermetropia, weak stereopsis, and poor fusional amplitude is particularly high. In an analysis of high school students Taylor,[23] found that among the good readers 41 percent were hyperopic and 15.5 percent were wearing glasses, while among the reading failures 67 percent were hyperopic and only three percent were wearing glasses. Ehlers[24] tested the velocity of vision with a photographic shutter, and demonstrated that the recognition of a blurred image takes longer than that of a sharp image. Kurtz[25] asked six subjects, aged 20 to 30 years, to read 150 words in fine type. After 30 minutes a similar passage was read with minus lenses to simulate hyperopia. A reduction of 24 to 74 words read per minute resulted.

Scobee[13] stated that: "Any procedure which refers half or more of the students who need care will give a high proportion of unnecessary referrals. . . . But it is far better to be safe than sorry." Lancaster and his collaborators[26] likewise agreed that it is preferable for school screening procedures to err in over-referrals than in under-referrals. But some school boards hold the opposite view, one spokesman saying: "It is wiser to miss some children than to refer too many who do not require treatment and thus lose respect for the screening method."

Sound practice requires that those who fail any screening test should be rechecked. The visual acuity of every individual fluctuates constantly about a mean value due to variations in the tear film on the cornea and the inconstancy of attention, fixation, and accommodation. Near vision is affected especially since the greater the accommodative effort, the less its exactitude. The repetition of visual acuity measurements, conducted by Bárány[27] with an automatic exposure time of two seconds, showed a variability of 20 percent—a variation equivalent to the difference between 20/20 and 20/25.

The transilluminated near-vision chart

The transilluminated near-vision chart is an interesting new development. The American model comes in a small attractive kit in which a variety of small slides can be inserted (fig. 1). The apparatus provides the

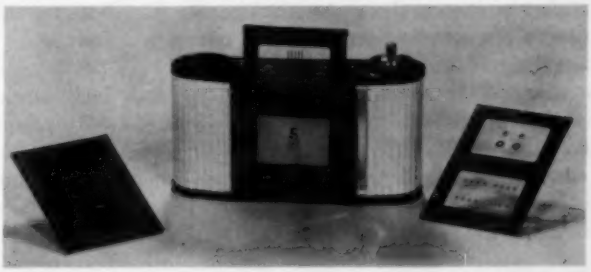

Fig. 1 (Lebensohn). Transilluminated near-vision chart (American model).*

interest of novelty and uniform brightness at any near distance, features that are particularly valuable in cases of subnormal vision. The small slides avoid distraction and stimulate attention. A duochrome slide is available, divided vertically into two equal parts, blue and red of definite spectral wavelengths. The duochrome far test is a standard feature of all projectocharts. In the near test the duochrome slide should not be superposed routinely over letters or numbers as in the far test since at near the difference in the brightness of the colors and the chromatic difference in magnification confuse the judgment. These difficulties can be avoided by using for the subjacent slide a grid of black lines or the Verhoeff circles.

These simple targets, which demand no literacy, permit a measurement of the refractive correction that induces an equal sharpness to the lines or circles under the blue and red. The blue and red were selected as being the purest spectral colors available. The blue focuses parallel rays at +1.25D. anterior to the fovea; the red at 0.75D. posterior. For an emmetrope, the symbols under the blue and red are equally sharp at 56 inches; but since equal sharpness at 14 inches gives 0.5D. plus overcorrection, an allowance for this must be made. Thus in a screening examination, if +2.0D. effects a balance in this duochrome test at 14 inches, the eye is +1.5D. hyperopic.

The test, which requires a darkened room, is a useful office procedure. Its helpfulness in a difficulty is illustrated in the following case:

A five-year-old boy had congenital bilateral ectopia lentis, each lens dislocated downward and temporally. Under atropine, only the aphakic refraction could be determined accurately by retinoscopy. The indicated correction was: R.E., +8.5D. sph. ⊂ +1.75D. cyl. ax. 75°, 10/50; L.E., +9.0D. sph. ⊂ +1.75D. cyl. ax. 105°, 10/50. In a postcycloplegic test two weeks later the aphakic correction gave the same acuity. At this time the phakic refraction was determined, using the duochrome test at 56 inches over a slide with two large E-s. The correction determined by these data and the astigmatic dial was: R.E., −4.0D. sph. ⊂ −0.75D. cyl. ax. 90°, 10/70; L.E., −3.5D. sph. ⊂ 0.75D. cyl. ax. 90°, 10/70. Consequently the aphakic correction, which gave the better vision, was prescribed with a bifocal add of +3.25D.

Tests of perception based on near vision

Weston[28] used a card with 256 Landolt rings showing the gap in eight possible positions. The subject was instructed to mark rapidly the circles having the gap in a prescribed direction. With the 1.5-minute gap quickness of perception reached a maximum at about age 24 after which an average annual decline of seven percent was calculated.

Drake[29] devised several charts to test the ability to discriminate small differences. In one chart the subject checked rapidly every small circle not centered exactly in a larger

* Marketed under the name, "The Prox-Illuminator," by Barnett Optical Laboratories, 3120 North Cicero Avenue, Chicago 41, Illinois. Available with batteries or for use with rheostat.

circle; in others, the symmetric spacing of two, three, or four small circles within a larger circle was the criterion and the slightest asymmetry was to be checked.

Though these tests are obviously influenced by factors affecting sharpness of resolution and vernier acuity, respectively, the investigators claim that they test something beyond visual acuity for near. They hold that such tests, conducted in the manner described, measure qualities of perception—a visual function not evaluated by clinical tests.

Final remarks

The value of the near test in screening procedures has not been sufficiently explored. In older children the test for near vision is somewhat more accurate than the screening for hyperopia in the Massachusetts Vision Test. In children under nine years both tests, as presently used, often give equivocal results. What modifications of the near test would increase the percentage of correct referrals can be determind only by further research. Investigation of the following items is suggested:

1. The preferable testing distance—10 inches or 14 inches?

2. The preferable target—reduced Snellen optotypes or unconnected words composed of small lower-case letters?

3. The illiterate test. Which is preferable—denoting the direction of isolated E-s or counting the E-s of a set in a particular position?

4. The transilluminated near-vision chart. The duochrome test at 14 inches using +2.0D. sph. is theoretically equivalent to the Massachusetts Vision Test. Which is more reliable?

5. Objective testing of visual acuity. Visual acuities between 20/200 and 20/10 can be assessed objectively with an accuracy of about 10 percent by an apparatus designed by Goldmann of Switzerland and described recently by Schmidt[30] in The Journal. In it a checkerboard panel moves to and fro at a rate of 40 times per minute. The apparatus is first viewed at 12 inches and the induced pendular movements of the eyes noted. The distance is gradually extended until the rhythmical movements cease. From the measurement at this end-point the visual acuity is computed. In young children who are unreliable in their subjective response this objective test may prove most useful.

In school surveys the near-vision test should supplement the hyperopia test. Subjective complaints, spontaneously volunteered, always merit attention; but symptoms elicited by questioning are often misleading.[13] When any doubt for the need of eye care arises, the child should be referred for an ophthalmologic examination which is the only safe guidance.

4010 West Madison Street (24).

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COMPRESSION ATROPHY OF THE OPTIC NERVE

With discussion of nerve degeneration and regeneration

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In the field of ophthalmology, there are several nerves coursing through constricted and unyielding channels where they may be subject to compression degeneration. The optic nerve may be compressed within the optic foramen resulting in atrophy with visual loss.*

The facial nerve may be compressed within the facial canal producing facial paralysis (Bell's palsy) affecting closure of the eyelids; the vestibular nerve in the labyrinth and internal auditory canal may be compressed (Ménière's disease) with the production of nystagmus with vertigo and other disturbances; and the trigeminal nerve and gasserian ganglion may be compressed within Meckel's cavity, a bony pocket covered with dura, resulting in sensory disturbances (tic douloureaux) affecting the eye and adnexa.

This discussion is confined to the optic nerve, except when it seems necessary to

* Nerve degeneration and atrophy may be produced when an adjacent expanding lesion, even in yielding tissues, exerts enough pressure finally to force the nerve against resistant surroundings; or to stretch it to such an extent that it can no longer yield. The constant hammering through the walls of a contiguous sclerotic artery may also produce nerve atrophy as, for example, arteriosclerotic optic atrophy.[1]

speak of nerves in general. The degenerative process and treatment of the optic nerve herein discussed can also be applied to the other nerves mentioned.

Upon occasion the ophthalmologist is asked to see patients who have severe cranial injuries and who, after returning to consciousness, complain of loss of sight in one or both eyes. Proptosis may be present with hemorrhage in the lids and conjunctiva. The pupils, at first, are usually equal in size. If the eye is blind, there is loss of light reflex. Dilated pupils usually indicate intracranial involvement.[2] Extraocular muscle paralysis may be observed. Ophthalmoscopic examination at first is usually negative. Visual field changes are not characteristic. In the absence of total blindness central and, more frequently, peripheral visual field defects are found. X-ray studies do not usually reveal fractures through the sphenoid bone involving the optic foramen. Pressure from dislocated foramen wall or direct injury from bone spicules are rare occurrences, although it has been repeatedly stated that loss of vision is usually caused by such fractures.

In some instances improvement of vision may begin about the third day and continue for a month or two, resulting in some impairment or in full restoration. On the other hand, if vision is not lost at first, it may begin to fail about the third day following the injury and continue to irrecoverable loss. These are the patients who are probably losing their sight as the result of compression atrophy. Finally, when permanent damage has taken place, ophthalmoscopic examination reveals pallor at the disc heralding optic atrophy. This pallor usually appears between the first and third week, occasionally later, as the distance of some five centimeters of intraorbital optic nerve lies between the point of involvement in the optic foramen and the papilla.

Heretofore, medical treatment for these conditions has seldom relieved the pressure which has been overcome only when atrophic shrinkage of the nerve has occurred. Surgery has been resorted to, with transfrontal decompression of the roof of the optic foramen giving possibly some slight measure of success, but only in selected cases, especially those showing X-ray evidence of the cause of the disturbance. In my limited observations, and the greater experience of others, especially neurosurgeons with whom I have talked, decompression rarely, if ever, has restored function. Perhaps surgical intervention has been too long delayed, but one must remember that the patient, most frequently seen following trauma, has just received a serious injury. He may have just returned to consciousness and may still be in the state of shock, not a good risk for intracranial surgery.

As has already been mentioned, by far the majority of patients have no roentgenologic evidence. In these cases the damage is the result of involvement of the soft tissues within resistant confines, and timely intervention with the relief of edema, removal of debris, and improvement of circulation may restore function.

In this discussion we are concerned with acute conditions, those in which there is sudden increase in bulk, and not the slower growing neoplasm or the chronic affections (example, syphilitic) which usually do not have edema as a major factor. In the majority of acute cases, tumefaction, with or without hemorrhage, is the first reaction. It is this I wish to emphasize as it may be overcome by proper treatment with retention or restoration of vision.

Examination of acutely damaged optic nerves from whatever cause, trauma or infection, reveals similar degenerative processes, depending upon the severity of the affection. The attempted repair and regeneration proceeds in a like manner irrespective of cause but influenced by tissue reaction. With less severe trauma or infection, the neuroglia of the nerve may be implicated, with sparing of the axons. There is found tumefaction of the oligodendroglia and astrocytes which undergo swelling and frag-

mentation. In the early stage this reaction may act as a protective buffer for the nerve fibers which, if the condition does not progress, may not be affected, the swelling resolving without impairment to function. However, if the swelling is extreme and in a confined space, it, in itself, may compress and damage the nerve fibers. With severe damage the nerve fibers undergo tumescence and degeneration with glial proliferation. Finally, there is atrophy of the axons with contracture of the glial elements.

In this acute involvement mesodermal tissues and cells play a part. The microglia assume phagocytic properties and the cell body undergoes swelling, its cytoplasm distended with products of degeneration. Hemorrhage from direct trauma and vascular or circulatory changes is frequent. In the acute stages polymorphonuclear neutrophilic leukocytes invade the area. All of these products of reaction increase the bulk which is further augmented in the presence of infection.

Degeneration involves the distal portion of the damaged nerve from the point of injury to its termination. There is also degeneration central to the point of injury that may extend to the cell body. In these stretches of nerve the mesenchymal elements proliferate. This is usually a great help in nerve regeneration as the sheath of Schwann forms parallel columns providing a path for the regenerating axis cylinders. Unfortunately the optic nerve, being in reality an association tract of the brain, has no sheath of Schwann, which is one of the reasons, according to a number of authorities, for the inability of the optic nerve to regenerate. Although Schwann's sheaths supply a means for parallel alignment present experiments seem to refute the idea of indispensable need of neurilemma cells for nerve fiber growth.[3]

In the process of repair, gliosis and fibrosis occur, the amount depending upon the type of lesion and the extent of damage. A clean wound from trauma produces less reaction and less scar tissue than an area severely injured, infected, or invaded by hemorrhage.

Regeneration begins in the intact proximal portion of the damaged nerve as far back as the nerve cell nucleus which must not be destroyed if regeneration is to occur. A form of pseudoperistaltic wave best describes the process which flows away from the cell down the axon.[4] The rate of progress depends upon a number of factors, such as size of nerve, distance from cell nucleus, and number of tributaries. Elasticity, plasticity, and rigidity, in other words resistance of adjacent tissue, also influence the progress.

Fulton[5] writes that a cut nerve regenerates at the average rate of four mm. in 24 hours. If the nerve is severed and in good apposition, eight days are required to form a union by bridging the gap preparatory to extension. Seven to eight days elapse before function reappears at the nerve terminal. A crushed nerve regenerates faster, about 4.5 mm. every 24 hours, due to continuity of its channel and less repair tissue. The latent or revival period of a crushed nerve with intact mesodermal structure is five instead of eight days.

Animal investigation has shown that in immaturity and the newborn, in the stage of development, there is orderly progress of axons to their predestined terminations. Their way is made easier through loosely formed and adequately vascularized tissue. This applies also to the optic nerve where experiments on young and newborn mammals have shown nerve fibers can regenerate, but with no consistency, and can function, at least in part.[6]

Unfortunately in humans this faculty of regeneration has not been found to apply to the optic nerve.[7] Regeneration following damage to the central nervous system of adult mammals has not been observed. Although there may be evidence of feeble attempts at axonal sprouting, degeneration takes place within a short period (abortive regeneration).[8]

There is apparently a need for a guiding pathway and, although the axons strive to proceed to their predestined terminals, their progress is made difficult, in fact, impossible, through heavy scar and the pressure of normal tissue, usually in the presence of an inadequate blood supply.

From these experiments and others, one has the impression that numerous contacts are made by regenerating fibers, but only those that are appropriate are maintained while the others undergo atrophy and absorption. Some are misdirected, coursing along blood vessels or other channels, and are lost and smothered in adjacent tissue, some become swollen and varicose, others meet the barrier head on and their efforts are foiled by dense scar tissue.

Clinical application

How can this investigation be applied clinically to benefit the patient who has suffered acute damage to the optic nerve resulting in loss of vision? If the nerve is completely damaged, there is not much hope for recovery in the light of our present knowledge. However, if the nerve is not completely damaged, the timely use of drugs to reduce edema, remove waste products, and improve circulation may save vision. Possibly the use of drugs reducing fibrosis and gliosis, thinning and vascularizing the scar, may enable regenerating axons to penetrate the barrier and succeed in reinnervation.*

This procedure has been undertaken by me in the few cases I have treated with some success. Similar treatment has been used also on patients with Bell's palsy, Ménière's disease, and tic douloureaux in which reduction of swelling and improved circulation appear to be efficacious. In those cases of Ménière's disease, where there may be interference with endolymph drainage, Diamox has also been tried and it has been found successful.

The medications used are:

1. For absorption of blood and removal of debris, fibrolytic and hemolytic enzymes.
2. For lessening and loosening fibrous and glial scar tissue, cortisone or ACTH. Piromen which is a polysaccharide-phosphate-ameno acid-lipid complex has been recommended, especially for its action on scarring, as it appears to produce a thin vascular instead of a thick collagenous and avascular scar.
3. For improving the blood supply, a vasodilator such as nicotinic acid.
4. To combat infection, a broad-spectrum antibiotic.

Summary

At the present time, regeneration after serious damage to the optic nerve in man has not been observed or reported. Lack of guiding pathways, inadequate blood supply, and dense scar are definite factors in the prevention of regeneration and reinnervation. Research and clinical trials have established the efficacy of fibrolytic and hemolytic drugs and also certain drugs to restrict and modify fibrosis and gliosis. If to these are added drugs to improve circulation and to prevent or relieve infection in the damaged area, there should be a greater probability of preventing loss of vision. Possibly when more work is done and more is known, vision, which has been lost following severe damage to the optic nerve, can be restored.

411 Oak Street (19).

* There is another substance desirable for the process of regeneration, and that is something that will stimulate neuronal growth. A neuronal extract recovered from central nervous system tissue has been used experimentally. The results show a great increase in speed of regeneration.[2] This is worthy of further investigation and clinical application.

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LATE CORNEAL DAMAGE FOLLOWING X-RAY THERAPY*

Report of two cases

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Varied sources of radiant energy have been utilized in ocular therapeutics, particularly in the treatment of malignant lesions and in epithelization of the anterior chamber, and, while extensive studies have been made on immediate damage to the ocular structures, there has been little in the recent literature describing the late complications of such treatment.

The two forms of radiant energy now most frequently employed in the treatment of ocular lesions are the beta-ray and the X ray. The former, provided by radium, radon, or the strontium-90 emitter, is chiefly of value in the treatment of superficial lesions since it has a low penetrability. X rays because of their greater penetration can be utilized in the treatment of both anterior and posterior segment pathology. Irradiation of the eye has been attempted for almost every known condition and has been particularly recommended for epithelial downgrowth, implantation cysts, dendritic keratitis, pterygium, vernal conjunctivitis, corneal ulcer, blepharitis, episcleritis, corneal vascularization, iritis, uveitis, hemangioma, absolute glaucoma, retinoblastoma, and metastatic carcinoma of the uvea. Since larger doses of irradiation have been shown to produce certain of these lesions, such as keratitis, uveitis, and corneal vascularization, the ultimate usefulness in some of these conditions is certainly open to question.

According to Cogan[1] there is no type of radiation, except radio waves on one end of the spectrum and cosmic rays on the other, which has not at some time induced an ocular lesion. The conjunctiva, cornea, and lens are relatively radiosensitive.[5] In the rabbit's eye Poppe[2] found the threshold dose for damage to the lens to be 250 r, with complete epilation and persistent changes in the conjunctiva and cornea with doses of 1,500 r. No pathologic changes were noted in the retina or optic nerve with doses of 3,000 r (175 kv., two mm. Al filter). Rohrschneider[3] also found the lens, conjunctiva, cornea, uvea, retina, and optic nerve to be decreasingly radiosensitive in the order given.

The clinical and histologic changes of the anterior segment shortly after irradiation have been well studied experimentally.

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Biegel[4] found no effects on the rabbit's cornea with less than 900 r from the betatron, while 1,800 to 2,400 r caused a fine superficial punctate haze in two to four weeks and 3,600 to 4,500 r resulted in corneal swelling, a ground-glass appearance, and anterior stromal vascularization in one to two months. Histologically he reported stromal edema and neovascularization with subepithelial cellular infiltration and epithelial thinning and vesiculation with pale-staining cytoplasm.

Cibis et al.[5] found iritis, aqueous flare, ciliary flush, and miosis in rabbits after 3,000 r, with similar swelling of the epithelial and endothelial cells. Hughes and Iliff[6] reported punctate corneal staining with edema after beta exposure, while the stroma exhibited vascularization and monocytic infiltration. Shaffer,[7] in an unusual utilization of an alpha emitter in an inclusion cyst, recorded detachment of Descemet's membrane, destruction of Bowman's membrane, and absence of the central corneal epithelium in addition to the foregoing findings. Others have noted inhibition of cell mitosis and loosening of the corneal epithelium[8, 9] with relatively low doses.

Wilson and Wilson[10] using Sr^{90} as a source of beta in dosages approaching 35,000 rep found corneal changes plus congestion and iritis after two to eight days, with vascularization, pannus, scarring, and even perforation for the next one to three months.

The effect on any of the tissues is of course dependent on the total dose, the time of exposure, the number and frequency of the exposures, the maturity of the cells, and the technique used by the operator. Variations in the latter factor explain some of the discrepancies in the response. While much of the experimental work has been done on the eyes of rabbits, it is believed that the radio response is quite similar to that of the human. It should be noted that there is considerable latitude in the dosages necessary to elicit a clinical response in normal tissues as reported by various observers.

Unfortunately, there is a good deal of overlapping between the recommended therapeutic and radiotoxic dose. This is well illustrated in the case of epithelial downgrowth where Maumenee[11] advises 700 to 2,400 r, Fleming[12] claims a 40 percent cure with 2,000 r, Merriam[13] recommends 2,000 to 3,000 rep and rarely 5,000 rep, Gallardo[14] feels 4,000 to 5,000 r is best. Sherman[15] states that 1,000 r is universally unsuccessful.

Specific case reports indicating ocular damage from irradiation are not as plentiful as experimental studies. One patient[15] treated with 5,700 r of X rays for retinoblastoma developed marked conjunctivitis, keratitis, ulceration, and eight months later perforation of the cornea coincident with an upper respiratory infection.

In 1936, Vail[16] described a well-documented case of epithelial downgrowth treated with radium (uncalculated dose) which developed corneal edema and vacuoles within one month, becoming progressively worse for 10 to 12 months, and then gradually gaining vision from 20/70 to 20/30 by the 15th month.

Merriam[13] enumerates the complications of beta radiation, describing conjunctival telangiectases (2,300 to 10,000 rep), limbal ischemia, scleral atrophy (20,000 to 30,000 rep), iritis, and iris atrophy occurring from three and one-half to 13 years later (20,000 rep), and superficial punctate keratitis lasting from four weeks (5,000 rep) to five months (20,000 rep) with corneal vascularization occurring up to 12 years later.

Reese[17] has also seen these changes following radiation of retinoblastoma after 2,500 to 6,000 r. He stresses the importance of keratinization of the conjunctiva and corneal epithelium as the initiating agent, precipitating or accelerating the superficial punctate erosions and xerosis.

It is of interest that surveys[18, 19] of the atomic survivors in Japan revealed only minor corneal denudation in patients so heavily exposed that they expired within a month.

Friedenwald et al.[20] have divided the ir-

radiation damage to the eye into two groups: Those that occur in one to three weeks after irradiation, the so-called "normal" or immediate reaction, consisting of hyperemia and edema with necrosis and proliferation; and the late reactions consisting of central superficial corneal opacities and in heavy doses complete opacity of the cornea. The late reactions they state as occurring from three months to two years after irradiation and producing changes which had at that time not been studied histologically (1952).

According to Duke-Elder,[21] the latent period may vary from a few days up to several years, representing "the time necessary for the injury inflicted at the time of radiation to develop into a change sufficiently gross to become apparent"; and he notes that telangiectases of the skin have shown a latent period of at least four years before making their clinical appearance.

Case reports

Two cases are reported which show what we believe to be late corneal changes following irradiation and occurring following a quiescent period of several years. One of these eyes was enucleated and the pathologic report is included.

Case 1

E. S., a 56-year-old white man, was admitted to Hines Veterans Administration Hospital in April, 1957, complaining of diminished vision and a scratchy type of surface irritation of the left eye for the past year. Interrogation revealed that the patient had seen many physicians and received many medications including cortisone for this discomfort. Systemic review was not remarkable except for a history of syphilis in 1917, treated with Salvarsan. Laboratory data, including STS, were normal.

Fig. 1 (Mann and Watt). *Case 1.* Left eye, showing cyst of anterior chamber and prominent vascularization in 1952, prior to irradiation. (Courtesy of Dr. T. Zekman.)

Fig. 2 (Mann and Watt). *Case 1.* Left eye, demonstrating corneal edema, updrawn pupil, and white sclera in 1957, four and one-half years after irradiation.

He had had a bilateral uncomplicated combined cataract extraction at Hines in 1942. Visual acuity was normal with corneal contact lenses and no further difficulty was encountered until 1952, when a cyst of the anterior chamber was diagnosed elsewhere. In November and December, 1952, 4,048 r of X rays (85 peak kv., no added filter, 1.5 mm. Al filter, 5 ma. at 15.5 cm. distance) in air were administered for the iris inclusion cyst in 10 divided doses. On April 11, 1953, his physician reported the left cornea as clear and visual acuity of 20/25.

At the time of admittance to Hines in 1957, his corrected visual acuity was $20/20 - 2$ in the right eye and 2/200 left eye.

Examination of the right eye revealed a normal aphakic eye with the exception of an unusual circumlimbal arrangement of U-shaped subepithelial vessels growing 1.0 to 1.5 mm. into the cornea. The remainder of the cornea was clear.

In the left eye the entire cornea was hazy and had a "frosted glass" appearance. The same vessels were noted in the periphery. The cornea exhibited diffuse punctate staining with central epithelial bullae. The iris cyst was just visible superiorly at the 12-o'clock position. There were no keratic precipitates and no demonstrable flare. The pupil was small and updrawn. Corneal and conjunctival sensitivity were diminished in the left eye.

The eyes were normotensive. Conjunctival culture from the left eye yielded a growth of Staphylococcus aureus, coagulase negative.

Therapy was attempted for 24 days, and con-

Fig. 3 (Mann and Watt). *Case 1.* Left eye. Sagittal section of anterior chamber with epithelial inclusion cyst.

sisted of topical antibiotics (30-percent sodium sulfacetamide, 0.25-percent Chloromycetin) and dehydrating agents (5.0-percent sodium chloride solution and 50-percent sucrose in methyl cellulose) in various combinations with no objective improvement. The feasibility of corneal transplant was discussed and rejected, and because of the persistent distress to the patient an uneventful enucleation was performed on May 17, 1957.

The pathologic study was performed by the Armed Forces Institute of Pathology. The report of W. M. Patterson, M.D., follows:

"The corneal epithelium is edematous and slightly irregular. The central area is now denuded. There is extensive although thin pannus formation extending over most of the anterior surface. There is remarkably little radiation effect on the subconjunctival vessels and the vessels in the pannus over the site of the cyst. There is a well-healed, vascularized penetrating wound of the cornea slightly distal to the ciliary body attachment on the side of the cyst. The anterior chamber is narrowed superiorly by a thin-walled epithelial cyst, but the remainder of the chamber is deep and free of foreign material.

"The iris inferiorly is thin and delicate except that a narrow zone of the anterior surface is covered by a thin layer of epithelium. The iris limb superiorly is fibrotic and some of the central portion is absent. On the surface of the fibrous proliferation in this region, and extending onto the anterior ciliary body and posterior cornea, is a very thin-walled epithelial-lined cyst measuring 2.5 mm. on section.

"The ciliary body is thin, and the processes hyalinized and shortened. The processes superiorly are drawn forward and incorporated in the fibrous reaction. The lens is absent. The retina is thin and shows extensive microcystoid degeneration of its inner layers. The ganglion-cell layer is not identified. The choroid is thin and free of inflammatory change. The sclera is not unusual. The nervehead is edematous and the lamina cribrosa is bulged forward. The neural elements of the nerve appear fairly well preserved.

"Diagnoses. (1) Postoperative state—intracapsular cataract extraction (remote); (2) epithelization of the anterior chamber (cyst); (3) radiation therapy for cyst; (4) keratitis following radiation."

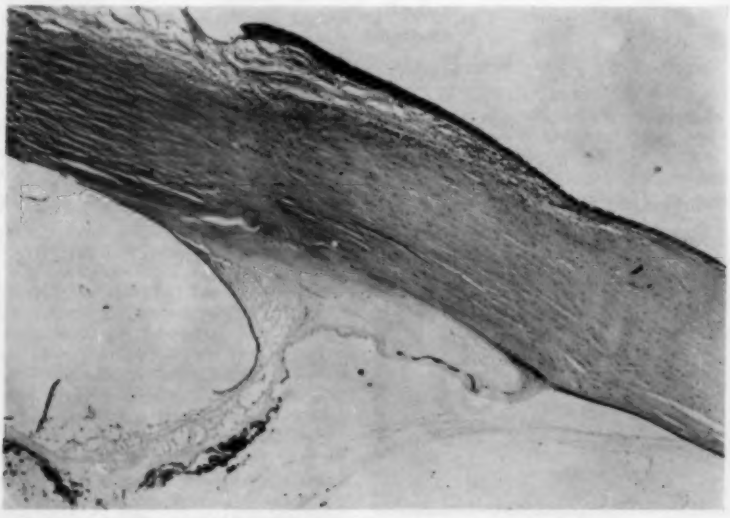

FIG. 4 (Mann and Watt). *Case 1.* Left eye. Close-up of inclusion cyst, erosion of corneal epithelium, subepithelial infiltration and vascularization, plus stromal edema.

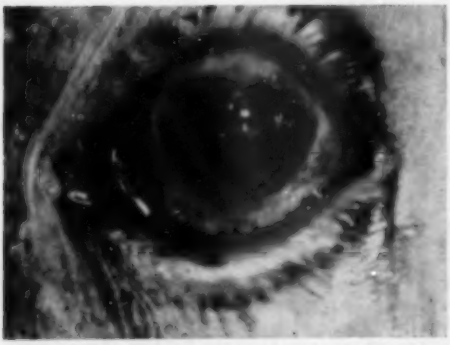

Fig. 5 (Mann and Watt). *Case 2.* Left eye, showing corneal and conjunctival edema. Appearance nine years after radiation and three years after onset of corneal and conjunctival edema.

CASE 2

Mrs. W. J. C., a 67-year-old white woman, was first seen in 1945 with bilateral senile cataracts. The following year visual acuity had been reduced to 20/100 in each eye and a cataract extraction was advised. On April 9, 1946, a right cataract extraction was performed with complete iridectomy. The capsule ruptured on delivery of the lens, but the remaining cortex cleared rapidly and on June 6, 1946, vision was correctible to 20/15 and a lens was prescribed (+10.25D. sph. ⊃ +3.0D. cyl. ax. 25°). It is of interest to note that there was a three-disc-diameter pigmented area below the right macula, not significantly elevated. This lesion has not changed during the past 12 years, demonstrating its benign character. The vision has remained good in this eye and the tension has been normal.

On March 29, 1947, an uncomplicated cataract extraction was performed on the left eye. The patient developed an acute gall-bladder attack while in the hospital but the eye remained remarkably free of injection. The anterior chamber reformed promptly. A correction for this eye was prescribed in June, 1947, resulting in a visual acuity of 20/15 (+12.25D. sph. ⊃ +1.5D. cyl. ax. 15°). Binocular vision was obtained, muscle balance tests showing two prism diopters of esophoria for distance and two prism diopters of exophoria for near. There was no pathologic alteration of the fundus. On July 12th, two and a half months after the extraction, the patient reported that the left eye had been red and uncomfortable. Tension was normal but an epithelial downgrowth was noted on the superior portion of the corneal endothelium.

X-ray treatment was advised and given under the direction of a radiologist, the dosage being 126 r on each of the following dates: July 15th, 18th, 22nd and 29th for a total of 904 r (140 kv., 25 ma., one mm., Al filter and 50 cm. distance; portal of entry 2.5 cm. diameter).

On August 28th, the Schiøtz tension was: R.E., 25 mm. Hg; L.E., 40 mm. Hg. There was a slight diffuse staining and edema of the left corneal epithelium but no ciliary tenderness. The downgrowth seemed thinner and had not advanced. Two-percent pilocarpine was prescribed which reduced the tension in the left eye to 17 mm. Hg (Schiøtz). The epithelial downgrowth never advanced further and the tension was controlled at all times with pilocarpine. The corneal changes subsided, but vision could not be improved to better than 20/200 due to a membrane in the pupillary area. A discission was done in September, 1948, with a good opening but no real improvement in vision. However, by 1950, vision had returned to 20/30 in this eye, tension was controlled, the eye was quiet, and all seemed stationary.

In March, 1953, nearly six years after the irradiation, there was a rather sudden onset of marked conjunctival and corneal edema which has persisted through 1957, although somewhat less severe in degree when last seen (November, 1957). The cornea has a reduced sensitivity, edema, diffuse stippled staining with fluorescein, and some diffuse corneal opacity with tendency to vesicular formation, but no vascularization. The conjunctiva shows hyperemia and edema throughout the bulbar portion. There has been no increase in the epithelial invasion as far as can be determined through the cloudy cornea and the tension is normal. Vision is reduced to hand movements in the eye and there is no pain. Various attempts to reduce the edema with cortisone, adrenalin, and 40-percent glucose in aquaphor were all without the slightest effect.

COMMENT

Although the dose of X-radiation received by the two eyes was at the extremes of the recommended therapeutic level, the gross changes induced by this radiation were remarkably similar. The 904 r administered in Case 2 is lower than the minimum recommended dosage of 1,000 r, yet it not only limited the epithelial downgrowth but caused a complicating radiation keratitis.

Thus the uncertainty of achieving effective tissue dosage and the variability of tissue response are emphasized.

SUMMARY

The immediate effect of irradiation on the eye has been well studied experimentally and clinically but the late effects have been rarely reported and apparently never before studied histologically.

Two cases of late damage from irradiation are reported. In one case the dosage of

X rays was reported as 4,048 r and the corneal changes occurred approximately three years later; in the second case the dose was but 904 r and the changes did not follow for six years.

The principal changes were edema of the conjunctiva and cornea, with multiple superficial staining areas in the cornea, clouding of the cornea with tendency for vesicles or bullae, and decreased sensitivity. Medical and symptomatic treatment was of no avail.

One eye was enucleated and the histologic findings are reported.

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ECTODERMAL DYSPLASIA

Report of kindred with ocular abnormalities and hearing defect

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Introduction

Primarily, this paper reports on a kindred of seven individuals in three generations, who showed the following ocular abnormalities: congenital and juvenile cataracts, some of which showed spontaneous maturation and absorption, and others spontaneous luxation with complications; basic myopia; fluid vitreous; and one instance of retinal detachment in the presence of a lens luxated into the vitreous. These patients also had defective hearing, a congenital defect of the nose and the associated facies, and other evidence suggestive that they may represent incomplete examples of hereditary anhidrotic ectodermal dysplasia. Therefore, consideration is first given to ectodermal dysplasia and some of its manifestations.

Ectodermal dysplasia

Definition

The condition, known previously as ectodermal defect, involves faulty evolution or anomalous formations of the ectoderm and its accessory structures. Often other physical characteristics are associated. Congenital abnormalities or absence of the hair, teeth, nails, and glands of the skin are frequent. The literature on this topic is large, but is found more in the fields of dermatology and heredity than in ophthalmology. Earliest reports of this condition were by Wedderburn in 1838, Thurnam in 1848, and by the American dentist Guilford in 1883.

Embryologic background

From the embryonic ectoderm are derived the outer epithelium of the body, and the neural tube. From the former develop the skin with its sweat and sebaceous glands, its hair, the nails, mammary glands, oral epithelium, tooth enamel, the olefactory epithelium and nerve, the anterior lobe of the hypophysis, the crystalline lens of the eye, the auditory vesicle, and inner ear mechanism. From the neural tube is derived the central nervous system, including the retina.

In any widespread defect of the ectoderm, one might expect to find abnormalities of any or all of these structures, including the lens, the retina, and even the vitreous, which is basically of ectodermal origin. In fact, most of the structures listed above have been reported affected in cases of ectodermal dysplasia or in associated syndromes. And yet, in the more purely ectodermal types, free of endocrine overlay, defects of the lens have not been reported, and defects in hearing only very rarely. Many of the structures derived from the outer epithelium of the body have also a secondary supporting investment of mesodermal origin (Patten) and some syndromes associated with ectodermal dysplasia exhibit definite changes in the bony structures.

Subdivisions and syndromes

1. *Hereditary ectodermal dysplasia*

In 1920, Goeckermann differentiated ectodermal dysplasia into a major anhidrotic type and a minor hidrotic. In the minor type the nails are short, thick, slow-growing, and sometimes absent. The hair usually is defective, being fragile and sparse. There may be a dyskeratosis or thickening of the palms and soles. This type is usually dominant, and, according to Clouston, must be fairly common in America, having come in from France over 200 years ago. But this type may also be only a modification of the major anhidrotic type of hereditary ectodermal dysplasia. While the major anhidrotic type is largely restricted to males, the minor hidrotic is transmitted by both sexes and

manifests itself through many generations (Thannhauser, 1946). In all of these syndromes, different grades of the defect, or variations in expressivity, may be found. Franceschetti (1953) has outlined an interrelationship of the ectodermal dysplasias.

2. *Anhidrotic ectodermal dysplasia*

The major type characteristically shows the triad of anhidrosis, hypotrichosis, and hypodontia. In some degree the patient is devoid of hair, ability to sweat, and teeth. The anhidrosis and intolerance of heat may be conspicuous, as in an infant with convulsions and high fever in summer heat, or only partially present and unknown to the patient. The sparseness of hair may be noteworthy if the lashes or brows are involved, or the scalp in females. All or only a few of the teeth may be missing, and those present conical and malformed; in severe cases dentures in childhood are a necessity. Skin is soft, dry, and feminine. Rarely the mammary glands are absent (Clouston, Osbourn). There may be congenital ozena, dysphonia, thickened cranial bones, skin wrinkles around the lids and mouth, and mental retardation. Rarely has defective hearing been reported; usually it is not mentioned (Helweg-Larsen). The anhidrotic type is rare, with somewhat over 120 cases described in the literature, of which 12 percent are female (Franceschetti, 1953). There is no endocrine imbalance in this syndrome.

As well described by Lewin, most patients with anhidrotic ectodermal dysplasia have an external nasal deformity, consisting of an unusual shortness of the nose, a flat bridge, and a lack of forward development of the maxillary bone or central face, producing a depression in that area sometimes termed a dish-face deformity. There is a shortening in the vertical dimension of the maxilla in the anterior half, as evident in careful X-ray studies of the skulls of my patients No. 6 and No. 7, but the height of the posterior half of the maxilla is normal. The roof of the maxilla is found to slant down as it comes forward. This explains the appearance which one author has termed "squashed" from above down, and another has called a bull-dog expression.

Another feature is the clinical absence of the nasal bones, often noted in reports of cases. Comparison of clinical impression with radiograms, however, reveals that the nasal bones are present, but, because of the backward displacement of both the nasal bones and the front of the maxilla, what, clinically, seems to be the palpable anterior edge of the nasal process of the maxilla, is actually the anterior edge of the nasal bone, in a more posterior position. The nasal bones may be a little small, but are not generally actually absent, although Horne, in an excellent discussion of the facies, states they were missing in his case.

A third feature of the facies, as noted by Thannhauser (1936) and confirmed in X-ray films of my two patients, is the prominence of the frontal bossae. These accentuate the flatness or depression of the bridge of the nose, and the saddle-bridge appearance that has so often led toward a diagnosis of congenital syphilis (Horne). In my patients the entire thickness of the frontal bone in the region of the supraorbital ridge was unusually great, so that this zone of the frontal sinuses, which, incidentally, were entirely missing in these two boys, protrudes and emphasizes the flatness of the nasal bridge. It could not be determined, in my cases, whether the thickening was more marked in either the inner or the outer table of the skull.

Published portraits of patients with this nasal defect show a strong similarity, despite some variations, and occasional question of whether an individual case should properly be labelled as an example of saddle-bridge. The nasal defect and facies are not present in the hidrotic form of ectodermal dysplasia. Yet it is not pathognomonic for the anhidrotic type, as it may occur in other conditions, such as congenital syphilis, gargoylism, achondroplasia, and even alone in an

otherwise normal body (Horne). It has been reported, but rarely, in the associated ectodermal syndromes.

Associated with the absence of glands in the skin, there may be an absence of glands in the mucous membrane of the nasopharynx, causing a congenital atrophic rhinitis or ozena, with foul discharge (Clouston).

Since bones are of mesodermal origin, Lewin has tried to explain the deformity of the maxilla in an ectodermal dysplasia by suggesting that there may be an early halting of the endochondral ossification of the skull in early childhood, related somehow to the (ectodermal) anterior lobe of the hypophysis. Another approach to an explanation would be to consider these syndromes to be not completely limited to ectodermal structures, but to be a polydysplasia due to a germ-plasm defect, and the facies to be due to a dysostosis of the bones of the face.

Some of these have recently been reviewed thoroughly by Urrets-Zavalia, who says, in trying to correlate a group of skull abnormalities on an embryologic basis: "No wonder, then, that, when faced with the bewildering variety of these, and similar defects, most observers give them little attention, regarding their multiplicity as merely accidental."

The mandible and maxilla are the two largest bones of the face. The latter is ossified in membrane from two centers which appear during the sixth week of fetal life. Generally the nose in Rothmund's and Werner's syndromes, as well as in progeria and in the Hallermann-Streiff syndrome, has been described as pointed and beak shaped.

3. *Rothmund's syndrome*

Several other hereditary syndromes are related to ectodermal dysplasia. Two of these are Rothmund's and Werner's syndromes, which have now been carefully differentiated one from the other (Franceschetti, 1949; Thannhauser, 1945). Rothmund in 1868 described "cataracts in association with a peculiar degeneration of the skin." The lens opacities appear in the first few years of life, bilaterally, and develop rapidly.

Characteristic skin changes start a few months after birth, known as livedo-cuticularis, and are a marmoration due to distended veins, later changing to a netlike pattern of telangiectases around small atrophic areas. According to Thannhauser (1945), in the differential diagnosis, skin changes are the most characteristic feature and are present in all reported cases. Except for these skin changes, the facies are not characteristic. There may be hypogonadism. Females are affected more often than males.

4. *Werner's syndrome*

In contrast, Werner's syndrome develops after puberty, between 16 and 30 years of age, with evidences of a premature senility that has caused Thannhauser (1945) to call this progeria of the adult. There is a progressive development of cataracts, premature canities, alopecia, and a sclero-poikiloderma type of skin atrophy of distal ends of the extremities, with ulcers. The facies show senile changes, the nose is beaked, the mouth and chin small. Stature is rather short, there is a tendency to osteoporosis and to diabetes, hypogonadism is frequent, and death common before the age of 40 years.

Both Rothmund's and Werner's syndromes, therefore, show cataracts, rather pronounced skin changes, and sexual underdevelopment, but the sweat and sebaceous glands in the skin are normal (Upshaw). Franceschetti (1953), Thannhauser (1945), and Upshaw give tables clearly differentiating the characteristics of these and associated syndromes. They are described here for the purpose of aiding in the proper classification of the kindred to be detailed later.

5. *Incontinentia pigmenti*

Another syndrome in the family of ectodermal dysplasia is incontinentia pigmenti,

first described by Bloch in 1925, which shows a bullous eruption on the body at or soon after birth, followed by pigmentation of peculiar pattern. It may be familial, and may be accompanied by ectodermal and mesodermal defects (Haber). Franceschetti and Jadassohn divide the disease into two separate syndromes, the type of Bloch-Sulzberger and that of Naegeli. Both have cutaneous pigmentation and dental anomalies. The former type has various ocular abnormalities and malformations occurring in 25 percent, such as cataract, optic atrophy, retrolental fibroplasia, retinal thickening, and detachment. The Naegeli type has diminished sweating.

Other related syndromes, according to Franceschetti (1953), are progeria, hereditary osteodysplasic gerodermia, and hereditary onycharthrosis.

Participation of the eyes

In ectodermal dysplasia and related syndromes, ocular defects are commonly reported in some, and seemingly quite absent in others. In Rothmund's syndrome, congenital cataracts are the rule. Rothmund's original report noted rapidly developing, bilateral cataracts, starting as starlike opacities at the posterior pole of the lens, and extending to the center. These formed, he said, from the ages of four to six years. Cole's two sisters had congenital, lamellar cataracts, and convergent strabismus. Otto Werner described four brothers and sisters under the title "Cataract in connection with scleroderma." The scleroderma is not of true type, but here again cataracts, of a juvenile or premature type, form in most patients, along with the early senescence that is characteristic of this syndrome.

In ectodermal dysplasia, of either the major or minor type, cataracts have been completely absent. In most case reports, the ocular findings have been scanty or absent. Nearly every report states, insofar as an ocular examination is performed and recorded, that the eyes were normal.

Upshaw stated "we have found in the literature no reference to congenital cataracts in connection with this syndrome, although the lens is of ectodermal origin and such an anomaly might be expected," and later "The lens, although undergoing separation from the ectoderm during this time, enjoys, to our knowledge, complete immunity."

Thannhauser (1946) said that "none of the numerous cases of ectodermal dysplasia of the anhidrotic and hidrotic type reported in the literature exhibited either cataracts in infancy or later life."

The two sisters with cataracts reported by Cole were later reclassified as Rothmund's syndrome. Cockayne found only one report, in his comprehensive work, associating microphthalmos with ectodermal dysplasia. While considering cataract and the ectoderm, it should be mentioned that an association of cataract with atopic dermatitis has been recognized for some time (Beetham).

As noted above, about a fourth of reported cases of incontinentia pigmenti show ocular anomalies. The eyes are generally normal in progeria. In the Hallermann-Streiff syndrome, cataract is frequent.

Clouston said that strabismus is frequent in the hidrotic type of ectodermal dysplasia. As noted above, Cole's patients had strabismus. In the kindred reported herein, several members appeared to have a convergent strabismus, but it was apparent rather than real, and due to a large negative angle of kappa. Changes in the vitreous are not described; as already noted, it is of basically ectodermal origin.

Hearing

Hearing has seldom been mentioned in the literature, at least defects in hearing have seldom been noted. Ellingson in two brothers found some hearing loss. The mechanism of hearing involves several structures, but some of them are of ectodermal origin, the actual tono-receptive mechanism of the ear being a ridge of modified epithelial cells in the cochlear duct (Patten). Congenital deafness

may be due to defective nerve connections, to imperfect development of the neuroepithelial receptors, or to faulty formation of the auditory ossicles (mesodermal).

Helweg-Larsen reports a kindred of 14 with anhidrotic ectodermal dysplasia, of whom at least four had defective hearing, with onset between the ages of 35 and 45 years, and this author notes that the defect may be on the basis of ectodermal origin of part of the labyrinth.

Central nervous system

Also, the central nervous system has almost never been incriminated or found defective in these syndromes. Upshaw said "although the anomalies are ectodermal, only rarely have definite defects of the nervous system been found in typical anhidrotic patients. Numerous have been mentally inferior, but the same genetic mutation is not held responsible for both anomalies." Klingmuller and Kirchhof described three brothers with typical anhidrotic type of defect, together with signs of systemic cerebellar disease resembling Friedreich's disease. There was evidence of neurologic disease in their ancestors.

Cataracts: Absorption and luxation

Spontaneous absorption

Cataracts have been mentioned above as being frequent or universal in Rothmund's and Werner's syndromes, but unknown in the basic ectodermal dysplasia. Spontaneous absorption of cataract has apparently not been noted in these syndromes. That the cataracts may develop rapidly in Rothmund's was realized by him, and other observers (Guillaumat and Maeder).

The spontaneous absorption of a cataract has been reviewed by Marlow, who found 129 instances recorded to 1952, and he added five. All of his five were in rather elderly adults. He commented "It is difficult to believe that absorption can take place through an intact capsule. A lesion of some sort seems essential, whether it be structural or chemical. The evidence presented here indicates that spontaneous absorption of cataract has been and still is a comparatively rare observation." The instances reported in the kindred here described should therefore be of interest. Ferrer had a boy with a somewhat similar story, and Ehrlich has written on the absorption of congenital cataract.

Further, as in the cases here reported, an absorbing cataract may frequently cause glaucoma. Flocks et al. have reviewed 138 cases of this, where the cataract was hypermature. In only 22 of the 138 enucleated eyes did they find evidence that the capsule had ruptured. They concluded that the degenerating capsule permits escape of liquefied lens cortex. This is absorbed by macrophages, which in turn swell, and block the angle of the anterior chamber. This phenomenon may explain the glaucoma in three of my patients.

Luxation

A lens luxated free into the anterior or vitreous chambers may be in its capsule or consist of the nucleus free of a torn capsule. This occurred in two of my patients, and possibly in their mother. If the lens is luxated backward, Duke-Elder (a) notes that "no reactive catastrophe may result, at any rate for a considerable time; but if forward and the lens is arrested in the pupil or dislocated into the anterior chamber a severe irritative and exudative reaction is invariably followed by secondary glaucoma. . . . A posterior dislocation is usually tolerated better, but eventually the vision is usually lost." Luxation of the lens can evolve, according to Duke-Elder (b), due to congenital, traumatic, or spontaneous origin; and the latter may be on a mechanical, inflammatory or degenerative basis. The two or three cases in this kindred show all three origins, plus the degenerative basis.

Kindred of seven patients

Pedigree of the kindred of seven individuals here reported upon is given in

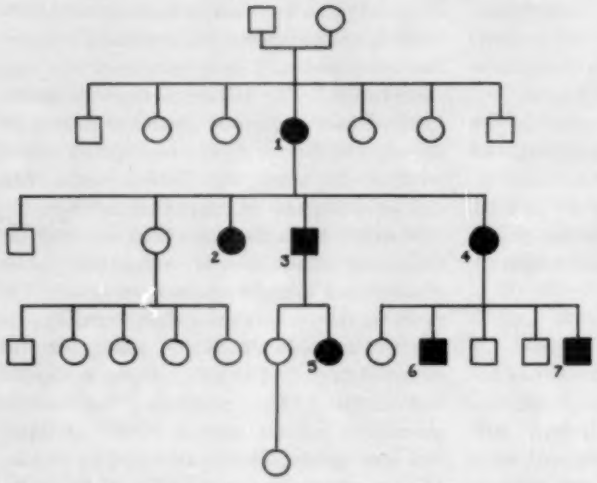

Fig. 1 (Marshall). Pedigree of kindred with ectodermal dysplasia: nasal defect with characteristic facies; cataract, myopia, and fluid vitreous; hearing loss.

Figure 1, and photographs of the living six follow. The family is unusually well versed in the characteristics of its members, so that questioning has established quite conclusively that no near blood relation possesses the unusual features of the affected seven.

The six living members have each had ocular surgery, most of it performed by me. All have had physical examinations. Sweating tests have been performed upon four of them, plus one normal female as a control. Complete skull X-ray studies have been taken on the two boys, No. 6 and No. 7. Careful otologic examination has been made of them and their mother, and elsewhere of two more of the kindred. Skin biopsy has been made on two patients, No. 2 and No. 5.

Several siblings, as well as all offspring of the affected individuals, have been examined. It is noteworthy that the siblings in both generations have no resemblance in facial expression to the affected ones. The unaffected individuals appear entirely average, normal, and even handsome. Among the affected six, facies, X-ray studies, otologic examination, and audiometer tests, sweating tests, and teeth are all so similar one to the other that the findings on one can properly be assumed to be similar and parallel in the others not subjected to the same special test.

The maternal progenitor, No. 1, in the first generation, is deceased, but much was learned of her by questioning her relations who had known and lived with her, and a thorough search among the relatives revealed none other who was affected.

Common physical characteristics in the kindred

For brevity, several characteristics of these affected individuals may be stated for the group, since they all possess them in similar degree. In stature and build they tend to be average, the females somewhat small and short, the males average. Personality is normal. Intellect is average, or in two instances slightly subnormal. Skin tends toward being soft, dry, and without much sebaceous activity. Hair is generally ample and normal, especially in the females, nor does it seem unusually fine. Many teeth are missing but most of them have been extracted, and there is no belief among the parents that there has been much variation from normal in the eruption or number of teeth. There are no definite anomalies of the nails. Ability to sweat is present, but diminished perhaps 25 percent below normal. There is no hypogonadism in either sex. The mothers nursed their babies normally.

Menses have been normal in onset and character in all females. Breasts and other sexual characteristics are normal. Facies are similar in all, and are shown in the photographs.

Ocular findings

In their ocular history as a group, probably none ever had quite normal vision. All were myopic until rid of their cataracts, after which they were two or three diopters hyperopic, indicating a basic rather than an index myopia. All had eyes of normal size, and with normal anterior segments. Intraocular pressure was normal until complications developed from cataract, luxation of the lens, or surgery.

All had fluid vitreous, proven at every operation in which the globe was opened, although a little formed vitreous was seen in two with the slitlamp. No formed vitreous ever appeared at operation.

The retinas were not definitely abnormal, but several observers described a peculiar pigmentation with prominent choroidal pattern, as is frequent in myopia. There were no localized retinal lesions, excepting only the single instance of detachment.

Due to a large negative angle of kappa, more than one examiner gained the impression from some patients that convergent strabismus was present, whereas, in all, the eyes were actually straight. There were no ocular palsies.

Among the six living members, one had a lens luxated by trauma (No. 3), another luxated with obvious spontaneous rupture of the capsule, at first backward, and later the nucleus into the anterior chamber (No. 4).

Of six eyes in the younger generation, five have shown sudden maturation of cataract, with glaucoma in three necessitating surgery (No. 5 and No. 6), and spontaneous absorption, without complication, of the cortex in the other two (No. 7). When aphakic, corrected vision has been about 20/40, and uncorrected vision has usually been very useful.

Hearing

Hearing is defective in all six living members. At one time or another each has used a hearing aid. No. 4, No. 6, and No. 7 have had audiometric determination of their hearing loss. Results on all three are surprisingly similar, and show about a 50-percent reduction from normal hearing. The same three have had careful otologic clinical examinations recently, which showed a clinical absence of the nasal bones in each, with a saddle type of nasal defect, and in one a polyp.

Radiographic studies

Careful X-ray studies were made of the facial bones of the two brothers, No. 6 and No. 7. Each showed a thickening of the outer table of the skull and absent frontal sinus. The height of the maxillary antrum was decreased in its front portion. The nasal bones were small, short, and far back of their normal position relative to the whole face. Orbital bone structure was normal and of average size for the age. Base of the skull, mastoids, and sella turcica were normal.

There was a saddle type of nasal deformity, with protrusion of the anterior upper teeth and marked thickening of the lips. Except for the protrusion, the teeth of No. 7 were fairly good. The tooth bud for a lower second molar was quite small, and a third molar was missing below. In the older brother, No. 6, the teeth showed various abnormalities. Extractions accounted for several missing molars. Two molar teeth in the right mandible were well developed but still unerupted and angled forward. The other teeth in the lower jaw were small and underdeveloped. The upper teeth, besides the anterior protrusion, showed marked overbite, and underdeveloped bicuspids. The molars were underdeveloped with the exception of one pair above. All teeth had abnormally small root structure in No. 6. Cuspids and bicuspids were small and abnormal in his jaws.

Sweating tests

Sweating tests were performed on No. 2, No. 5, No. 6, and No. 7. A similar technique was used on each. Heat was applied by infrared electric bulbs in a cradle over the trunk, the rest of the body being tented under a blanket. For eight to 13 minutes a high heat of 480 watts was used, following which wattage was reduced to 240 for seven to 20 minutes. Oral temperature was followed, and showed little change.

Twelve areas on the left side of the body were painted with Miner's iodine solution and dusted with starch. Sweating occurred at every site, except for the neck of No. 6, and it was nearly zero for the upper and lower arm of No. 7. Beads of sweat were noted on the brow of No. 5 and abdomen of No. 6, but none on the other two. The maximum amount of sweating at each site was recorded, judging by the number and size of discolored spots, and the degree of discoloration of the indicator site.

Sweating was distinctly less on the neck, upper chest, and arms, and greatest on the palm and in the axilla. But of significance was a comparison of tests on these four with results of the same test, recorded in the same way, run on a normal female of 32 years. In the upper half of the body her sweating exceeded that of the four patients in a ratio of 2:1, while in the lower body the ratio was about 3:2. Thus the patients showed, in comparison with a normal individual, a definite hypohidrosis, though far from anhidrosis.

Biopsy of the skin was performed on two patients, No. 2 and No. 5. Both were from the arm, and both showed no pathologic change, though in No. 5 the report noted that "only very occasional sweat glands were seen, as well as a small number of hair follicles."

Individual case reports

For brevity, the clinical story of each of these seven patients in the kindred is condensed, to include only the more important and positive findings and events.

No. 1, the maternal progenitor, was the only one of seven siblings who showed the short, defective nose characteristic of the affected individuals in the kindred. Born with defective vision, she wore glasses at the age of six years. Her left eye was blind at the age of 22 years, and the right at 38 years, presumably from cataract. At 42 years of age the right cataract "broke." For 10 years vision was only light perception. At the age of 51 years, after a fall, vision returned to each eye. Thereafter she had good vision without glasses until her death at the age of 78 years. This lady was not examined, but wrote this history herself, and it is confirmed by her many relatives. A group photograph shows the considerable difference in her facies from those of her completely normal siblings.

No. 2, an unmarried daughter of No. 1, at the age of 24 years (1944) was examined at the University of Michigan Hospital, where vision was found to be 12/200 in each eye, correctible to 20/100 by −8.5D. sph. ⊃ −3.25D. cyl. Each eye had vitreous opacities, a myopic conus below, thin retina, and prominent choroidal vessels.

At the age of 26 years, she was treated for an ovarian cyst, and the next year a laryngeal polyp was removed. At the age of 28 years, she had fever of undetermined origin intermittently for two years, and in 1949 returned to the University of Michigan Hospital. The eyes were not significantly changed. The nose showed a depressed, saddle-bridge defect, with septal deviation. There was a right hearing loss. Complete systemic and laboratory examinations were otherwise negative. Diagnoses were made of myopia, nerve deafness, psychoneurosis.

Right vision began to fail further starting at the age of 30 years. At the age of 32 years (1951) best corrected vision was right eye, 20/100, and left eye, 20/50—1. The right lens showed nuclear sclerosis of senile type; the left had a tiny posterior polar opacity. The fundi were of myopic type, and vitreous strings were visible. A year later vision was worse, and the cataracts had advanced. The left lens showed early opacities in the adult cortex. Tension was (Schiøtz): R.E., 14 mm. Hg; L.E., 16 mm. Hg.

On October 28, 1952, the right lens was extracted in the capsule under general anesthesia. There were no operative complications, but the globe was very soft before corneal incision, with specks of blood visible on the iris base. A large air bubble was trapped. On the first postoperative day, a small hyphema was noted; on the second, a large layer of blood was visible in the posterior vitreous space, lining the retina; on the third, there was continuous pain in the eye and tension was 45 mm. Hg, and it ranged for two weeks between 16 and 46 mm. Hg. By lying on her face, the blood ran to the anterior chamber, but there seemed to be no fresh bleeding.

On November 15th and again on November 20th paracentesis and irrigation of the anterior chamber were performed, because of the high tension. Ten-

Fig. 2 (Marshall). *Patient No. 2,* aged 38 years. Juvenile cataracts surgically removed, with postoperative glaucoma right eye.

sion rose soon to 64 mm. Hg, so on November 27th a cyclodialysis was performed; on December 7th a trephination, and on December 17th a cyclodiathermy. The anterior chamber was deep.

Intraocular pressure was intermittently controlled with di-isopropyl-fluorophosphate (DFP), but on January 3, 1953, a second trephination was done because tension had risen to 68 mm. Hg, and on January 17th a third trephination. None of these operations was effective in lowering tension for more than 10 days. No trephination blebs existed over a few days. Miotics were continued for six months, but thereafter the tension remained normal. In March, 1953, the right eye with +3.0D. sph. ⌒ +4.25D. cyl. ax. 125° saw 20/50—1, and, in 1955, 20/40—1, which has persisted.

In February, 1955 (aged 34 years), the left eye could only count fingers, so the left lens was removed using the same technique, without surgical or postoperative complications. A year later this left eye had corrected vision of 20/30. Tension was: R.E., 16 mm. Hg. and L.E., 17 mm. Hg. Blood Kahn on all hospital admissions has been negative.

No. 3, a son of No. 1, married with two offspring, was born in 1905 and had worn glasses since the age of 12 years. Hearing had always been poor. Vision had begun to fail at the age of 35 years, with the left eye blind at the age of 40 years and the right a year later. He had once been a truck driver.

In 1946 (aged 41 years) best corrected vision was: R.E., 20/200; and L.E., moving objects. The right lens showed advanced nuclear sclerosis and iridodonesis. The left lens was white and completely opaque. The right pupil was larger and oval. Tension was 14 mm. Hg in each eye. At the University Hospital, a left, extracapsular cataract extraction was performed, with considerable difficulty when the globe collapsed because of fluid vitreous. Endophthalmitis developed and the globe was eviscerated a week later. B. pyocyaneous was grown from intraocular discharge.

Physical examination at this time showed nothing unusual except for bilateral mixed deafness, with nerve involvement most marked, saddle type nose with some septal deviation, some polypoid degeneration in the nose with associated chronic rhinitis, and pyorrhoea alveolaris. Blood count, blood Kahn, urine, chest film were all negative. Fasting blood sugar was 69 mg. percent, without evidence of diabetes.

A year later (aged 42 years) he fell, striking and cutting the right upper lid, and the following morning the right eye had vision. Three days later examination showed a deep anterior chamber, tremulous iris, clear media, normal disc, myopic crescent lateral to the disc, and an opaque gray lens behind the iris at the 8-o'clock position, which occasionally rolled across the pupil. Vision was 20/200, or, with a +2.25D. sph., 20/60—1, and later 20/40. Occasionally he had to roll the eye to clear the visual axis of the obstructing lens. There were a few vitreous opacities. Two months after the accident he was removed from the Blind Aid rolls.

Nine months after the accident (April, 1952), the retina on the temporal side became detached, with a tear at the 9-o'clock position in the vicinity of old pigment clumps. The lens lay loose on the retina below. The aqueous contained specks and showed a faint flare. A diathermy operation was performed, which reattached the retina. A month later corrected vision was 20/70.

Eighteen months after this surgery, an emergency appendectomy was performed but it showed no acute process in section, and intraocular pressure was then found to be 65 mm. Hg and the next day 74 mm. Hg. For a few days it was controlled with miotics and corrected vision was 20/50. There were a few keratic precipitates, and some formed vitreous could be seen. Diagnosis was made of iritis with secondary glaucoma, due to absorbing cataract; this was the first time that true vitreous was seen and iritis proven.

Fig. 3 (Marshall). *Patient No. 3,* aged 52 years. Left evisceration following cataract extraction and endophthalmitis. Right cataract luxated back by trauma, retinal detachment surgically cured, eye then blinded by glaucoma.

The patient now did not return for seven months but during this time he noted periods of halos and blur. Corrected vision was still 20/50, there was no iritis, and the disc was normal, but tension was 63 mm. Hg. On miotics it ranged between 14 and 63 mm. Hg and the disc developed a large, shallow cup. Gonioscopy was inconclusive.

On acetazolamide and DFP tension ranged between 21 and 78 mm. Hg. Surgery was advised, but for several weeks the patient remained at home, ran out of medication, soon was blind, and then returned with a tension of 82 mm. Hg. A scleral trephination was performed.

During convalescence there was extensive choroidal detachment, the eye was mushy to palpation, and the trephine bleb soon healed flat. A month later vision was 20/200, there was no filtration bleb, and the disc was very pale. Six months later (July, 1956, aged 51 years) vision was barely perception of light, tension was 82 mm. Hg, the disc was cupped, the lens lay below on the retina. Medication reduced the tension to 26 mm. Hg but it rose again, and the patient did not return.

No. 4, sister of No. 2 and No. 3, was sent, at the age of 16 years (1927), to the University of Michigan Hospital for a mild postural scoliosis and markedly pronated feet. The Dermatology Department got a history of lifelong, progressive deafness, visual difficulty since the age of seven years, and, finding a saddle-nose and other stigmas of deviation, made a diagnosis of hereditary lues and treated her with arsphenamine, mercury rubs, and potassium iodide.

Otologic examination showed marked saddle nose, the bridge being almost level with the canthi, poor breathing space, and congenital bilateral nerve deafness. Dental examination showed only a few caries. Ocular examination showed only high myopia, vitreous opacities, and a corrected vision of 20/200 +1, bilateral. Two Wassermann tests on the blood, as well as on the spinal fluid, were all negative. Gold sol and mastic curves were flat.

At the age of 27 years (1938) she returned because of failing vision. The eyes were straight, but a large negative angle kappa gave an appearance of convergence. Each lens showed posterior polar cortical and subcapsular opacities, with granular opacities throughout the lens. These resembled those of complicated cataracts. There were vitreous opacities, and the fundi were of myopic type, with a temporal myopic crescent, a mottled macula, and prominent choroidal pattern, but no gross retinal lesions. With a −12.5D. sph. and low cylinder each eye had an acuity of 20/100+2.

Four years later (1942) each lens had a sclerosed nucleus, and the left lens was entirely opaque. Corrected vision was 3/200 and moving objects. The left lens was needled at the University Hospital but it was hard, did not fluff, and five days later the nucleus was removed by extracapsular method. Blood Kahn test, routine laboratory studies, general physical examination, neurologic examination, all revealed nothing new, and were negative.

Four months later the left eye with +2.25D. sph. ⊃ +1.5D. cyl. ax. 3° had acuity of 20/100+2, and with +2.5D. add read J1. Two years later (1944) a thin capsular secondary cataract was needled in this left eye, and corrected vision was then 20/40−1.

At the age of 43 years (1954) the right lens was a dirty gray, entirely opaque, and the iris tremulous. The left eye with +1.75D. sph. ⊃ +2.0D. cyl. ax. 3° saw 20/30+, and with add could read J2 well. The left eye uncorrected could see 20/200. The anterior chambers of the two eyes were equal in depth.

At the age of 46 years (January, 1957) the right eye had only light perception and good projection. One day, on raising up after stooping, the right vision improved to the ability to count fingers. But for a month the eye had attacks of pain and she of nausea. She was finally forced to come in because of the severity of the symptoms. The right anterior chamber was deep, and filled with cells in motion. Intraocular pressure was 17 mm. Hg (Schiøtz). The lens capsule hung like a wavy curtain behind the pupil and the gray, oval, lens nucleus could be seen in the anterior vitreous space below. The eye was treated with topical prednisone drops and atropine. Tension rose to a high of 33 mm. Hg. Atropine was stopped. Tension then remained normal and the iritis slowly quieted.

Four months later a discission of the capsule was attempted but the capsule readily tore free ahead of the blade and was lost in the fluid vitreous. Three days later corrected vision was 20/50. Two weeks after the discission, after stooping far forward, the right eye began to ache, and became so painful that she came in two days later. A small, sclerosed lens nucleus lay in the angle of the right anterior chamber. Tension was only 17 mm. Hg but the corneal epithelium showed edema and Descemet's membrane was wrinkled. The nucleus was removed from the anterior chamber, held by an erisophake, two hours later.

Three months after this operation vision was: R.E., +0.75D. sph. ⊃ +1.75D. cyl. ax. 100°, 20/40, J2 with add. Vision was occasionally transiently

Fig. 4 (Marshall). *Patient No. 4,* aged 47 years. Juvenile cataracts, the left removed surgically, the right removed after spontaneous luxation.

blurred when the capsule floated across the visual axis. Angle kappa was now zero, each eye; the eyes were straight. Tension was 23 and 25 mm. Hg. Kline test on the blood was negative.

No. 5, only affected daughter of No. 3, developed pain in her right eye at the age of 13 years. The pain grew worse and she was nauseated. The next day the pupils were found to be equal and active but the tension of the right eye was 68 mm. Hg.

The aqueous of the right eye was filled with white strings and specks and the right lens was opaque, though not densely so. The left eye was normal except for a small, central cataract. The right anterior chamber was deep and the lens was in normal position. Miotics lowered the pressure temporarily, then it rose to 73 mm. Hg so that, four days after the onset of symptoms, a right extracapsular cataract extraction was performed. This was in 1954, and experience with her cousins was valuable in recognizing that the cataract had somewhere broken through its capsule and in anticipating fluid vitreous.

At surgery, no normal vitreous was encountered. The globe collapsed and was repeatedly blown up with saline because of steady seepage of fluid vitreous. The lens repeatedly came loose from an erisophake; the zonule could not be ruptured, and, finally, the capsule tore so that the lens was removed in bits and pieces and the main portion of it fell back into the vitreous space. This space was freely irrigated with saline. After tying of sutures, the globe was blown up with saline and air. It healed well, with a few chunks of cortex temporarily in the anterior and vitreous chambers.

Three years later visual acuity, was: R.E., with a +0.5D. sph. ⊃ −0.75D. cyl. ax. 30°, 20/50, with add of +2.25D. J3 at a distance of 13 inches, or she could read the same five inches away without a glass. Tension was: R.E., 24 mm. Hg; L.E., 23 mm. Hg. The aqueous of the right eye was black. The left lens showed a Y opacity on the anterior surface of the nucleus, and a capsular paperlike opacity at the posterior pole.

Fig. 5 (Marshall). *Patient No. 5,* aged 16 years. Spontaneous maturation of right cataract, then surgically removed because of glaucoma. Left congenital cataract.

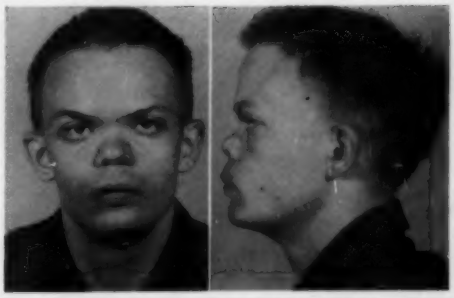

Fig. 6 (Marshall). *Patient No. 6,* aged 21 years. Spontaneous sudden maturation of each cataract, followed by partial surgical removal because of glaucoma.

No. 6, one of two affected sons of No. 4, was first seen when five and one-half years old, in 1941, and was the first of this kindred to come to my attention and care. The boy showed a central, posterior opacity of each lens, or bilateral congenital cataract, a bilateral weakness of the superior rectus, and a visual acuity of perhaps 20/300 in each eye. Five years later the lenses were similar, and with a −10.0D. sph. vision was 20/50 with each eye. A month later, the right eye became injected, he had a headache, and felt ill.

Examination of the right globe showed severe limbal flush, a deep anterior chamber with a few cells, an active round pupil, and a milky, nearly mature cataract. Tactile tension was elevated a little. There were many discrete, gray strands floating in the aqueous the next day, and the lens looked luxated backward a little. Tension swung between 20 and 50 mm. Hg on atropine and, later, miotics. The entire lens was opaque and the white fibrils moving in normal circulation of the aqueous were numerous. No tear in the capsule was visible.

Because the tension could not be controlled an extracapsular extraction of most of the right lens was performed about five weeks after the onset of symptoms. The globe collapsed because the vitreous was fluid but convalescence was uncomplicated. Three weeks after surgery on the right lens the corrected vision of the two eyes was each 20/100−1, but the right eye took a +1.0D. sph. and the left −10.5D. sph. Five months after surgery right corrected vision was 20/60 + 2, and a year later 20/50−1.

Two years after the right eye had become inflamed and painful (1948) the left eye did the same thing, with vomiting. Tension was found to be 60 mm. Hg. The cornea was edematous, chunks of cortex, larger than cells, floated in the aqueous, the lens was gray, and the pupil round and active. The iris was not tremulous, although the lens looked displaced back. Fibrils floated in the aqueous. Miotics lowered the tension only temporarily, so that, 10 days after the symptoms started in this left eye, extraction of the lens was attempted but

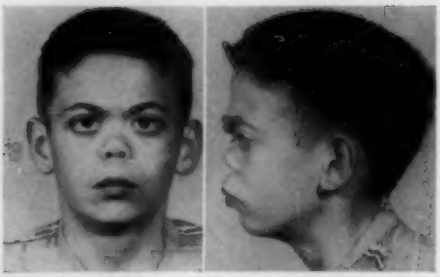

Fig. 7 (Marshall). *Patient No. 7,* aged 13 years. Spontaneous sudden maturation and absorption of each cataract; discission later.

it luxated back to the equator and further attempts were abandoned. Vitreous was fluid. Healing was smooth.

At the age of 18 years, the right eye took −0.5D. sph. ⊃ +0.5D. cyl. ax. 140° to see 20/50 +1, and the left eye took −0.75.D. sph. ⊃ +2.0D. cyl. ax. 42° to see 20/60 + 3. Uncorrected vision was nearly as good. With add he could read J7. Angle kappa was negative in the right eye. The eyes were straight but diverged under cover. There was myopic degeneration lateral to each disc. Corneas measured 11 and 11.5 mm. in diameter. The fundi were typically tigroid, myopic in type, with a crescent lateral to each disc, and a prominent choroidal pattern but without any pigment clumping. No lens was visible in either eye but, in the left, a strand of lens capsule was recognized. At the age of 15 years, IQ had been determined as 71. At the age of 21 years, the lad is a good citizen and holding a steady job.

No. 7, younger brother of No. 6, has a somewhat similar story, but without the complication of glaucoma. At the age of seven years, after several days of headache and ocular pain, it was noted that the left eye was blind and the left pupil white. Past history included rheumatic fever for three years.

My examination showed (July, 1951) a large negative angle of kappa, which exaggerated an appearance of convergence, and vision was only ability to count fingers with the right eye and perceive light with the left. The left inferior oblique was overactive. Globes were prominent. There was no iridodonesis but each lens looked posterior to its normal location. The left lens was opaque throughout, with water clefts. The right lens had a dense opacity at the posterior pole, plus thin capsular opacities throughout. A grossly normal right fundus was visible. That eye took a −20.0D. sph. but could not see 20/200.

Slitlamp examination showed some vitreous fibrils in the right eye. Light projection with the left eye was excellent and tactile tension was normal. Aqueous was clear in each eye.

Nine days after the first examination, the white pupil was changed and the left eye could see. Examination the next day showed specks and a few strings in the left aqueous, slight ciliary tenderness, small and active pupil, normal tactile tension, opaque capsule but some fundus reflex, and vision of counting fingers at two and one-half feet. A month later the right eye with a −20.0D. sph. saw 20/200; the left lens was absorbed with a nearly complete dense secondary cataract.

About 10 weeks after the first examination (September, 1951) the right eye was a little red and the vision worse. Examination showed a slight flush, small and active pupil, a complete cataract with no fundus reflex. The right aqueous had specks and strings in it. The left aqueous was clear except for a few cells, and there was a complete secondary cataract. The right lens showed many water clefts and the eye for a five-day period was mildly painful.

Two weeks after onset, the right aqueous contained many snakelike fibrils of various lengths, and chunks of cortex could now be seen in the anterior vitreous, and there was a faint fundus reflex. At no time was an opening visible in the lens capsule of either eye.

Three weeks after onset, the right eye could count fingers at six feet without glasses, and, five weeks after, each lens looked to be completely absorbed leaving a complete capsule or secondary cataract. Corrected vision was hardly 20/200 with each eye. The eyes were straight but looked convergent. Vitreous fibrils could be seen with the slitlamp in each eye.

Nearly eight months after the onset of symptoms in the left eye (February, 1952) a discission was done on each capsule. Since then uncorrected vision has been 20/200 in each eye: R.E., with a +1.75D. sph. ⊃ +1.75D. cyl. ax 95° now sees 20/30; L.E., with a +0.5D. sph. ⊃ +2.0D. cyl. ax. 65° sees 20/50; with an add of +2.5D. he can read J3. IQ has been determined as 97.

Classification of this kindred

I have been uncertain how properly to classify this kindred. I am reminded of, and sympathetic with, a published letter from Cole, who said "This is a perplexing etiologic subject. There have been so many variants and formes frustes that physicians can hardly keep ahead of the race." From the facies of these seven patients, with the typical nasal defect; their cataracts; their defect in hearing; and their mild defect in teeth and in sweating ability, there would seem to be no doubt but that the group definitely shows an ectodermal defect. It is hereditary and familial and known to be present in three generations. It seems to

have developed as a dominant characteristic, not sex-linked.

The congenital cataracts in patients No. 5, No. 6, and No. 7 suggest the possibility that their condition might be classified under Rothmund's syndrome, for they have had congenital cataracts that showed rapid development. However, they show no other signs of Rothmund's disease, no skin changes, no pigmentation or atrophy anywhere on their bodies, and they never have shown them. Nor do they show any endocrine disturbances or sexual hypoplasia. The presenile cataracts in patients No. 2, No. 3, and No. 4, and perhaps No. 1, suggest that they might have Werner's syndrome. But they show no skin changes either, or ulcers or hyperkeratoses; they show little evidence of premature senility or of alopecia, no endocrine disturbances or hypogonadism, no diabetes, no shortening of their life span, and they do not have the physical habitus found in Werner's disease. Only the cataracts would place this kindred in the syndrome of Rothmund or of Werner.

Mentioned only to be immediately discarded as inapplicable are the related or somewhat similar conditions of incontinentia pigmenti, progeria, gerodermia, dysplasias of nails and bone, Hallermann-Streiff syndrome, Marfan's and the Marchesani syndromes.

This leaves us with the classification of ectodermal dysplasia. Within this the minor or hidrotic type has nothing in common with the kindred herein described. The hidrotic type universally has thick and abnormal nails, may have hyperkeratoses, and lacks any characteristic facies, factors the opposite of those in this kindred.

This kindred lacks the triad found basically in the major, anhidrotic type of ectodermal dysplasia: hypotrichosis, hypodontia, and hypohidrosis. There is some evidence of the presence of the latter two conditions, but this is not strongly convincing. However, all seven members have the short, depressed nose and the underdeveloped maxilla and facies which are widely recognized and often portrayed as occurring with great frequency in that syndrome. This kindred seems to have the facies of one syndrome and the cataracts of two others; they seem to fit properly in no presently established clinical grouping.

Franceschetti (1953) has noted that ectodermal dysplasia is a typical example of a gene that is very variable in penetrance, specificity, and expressivity, which explains the formes frustes, and the abortive cases that show only one or another of the cardinal symptoms. One wonders whether the syndromes should be as sharply demarcated as authorities represent them.

It is suggested that this kindred represents an incomplete manifestation of hereditary anhidrotic ectodermal dysplasia. If that classification is correct, they are perhaps the first reported to show associated cataracts and among the very few reported to have an associated hearing defect. If that classification is incorrect, an alternative is to consider this kindred as showing a new combination of characteristics: the facies and some hypohidrosis and hypodontia of anhidrotic ectodermal dysplasia; cataracts resembling those of Rothmund in one generation and those of Werner in another; and a hearing defect that has seldom before been reported.

Summary

As background for a detailed report on a kindred of seven patients, review is given of the occurrence of ocular and hearing defects in the major divisions of ectodermal dysplasia. In the kindred the following conditions were noted: (1) Nasal defect and facies characteristic of the anhidrotic type of ectodermal dysplasia; (2) congenital and juvenile cataracts; (3) myopia and fluid vitreous; (4) spontaneous, sudden maturation and absorption of congenital cataract; (5) luxation of cataract; (6) congenital hearing loss. Although an ectodermal defect is obvious, further classification of this kindred is uncertain.

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THE SURGICAL COMPLICATIONS OF PRIMARY GLAUCOMA

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Practically every issue of our ophthalmic journals contains one or more articles relating to glaucoma. The research laboratories are endeavoring to unravel the causes of the increased intraocular pressure, and also to explain the modus operandi of some of our therapeutic agents. There have been comparatively few communications concerning the complications of glaucoma surgery. It is not the purpose of this paper to discuss the pros and cons of medical versus surgical therapy, but rather to present the complications that may occur, and describe how, in my opinion, they should be handled.

As in any type of surgery, the patient should be advised of the necessity of the operation. A few minutes of explanation should be given, and a frank discussion of the outcome held with the patient and preferably a member of his family. The patient should not be promised a miraculous cure, and—with the exception of acute congestive glaucoma—he should be told that his vision will be no better, and may even be worse. One sees many disappointed patients who have had successful tension-lowering procedures, but who, because their problem was not made clear to them, continue to berate their ophthalmologists.

Acute congestive glaucoma

It is generally agreed that, with only the rare exception, acute congestive glaucoma should be treated surgically. Prior to surgery, every attempt should be made to reduce the intraocular pressure to normal by medical means. Diamox is of considerable value but only as a preoperative adjunct. Should the intraocular pressure be quickly controlled, it is surely preferable to wait 24 to 48 hours to allow some of the congestion to disappear before performing surgery. During the period, miotics alone should be used, and should the tension rise, surgery should be resorted to immediately.

Except as initial therapy, Diamox has no place in the treatment of narrow-angle glaucoma.[1] I recently saw a patient in whom, during a subsiding attack of acute glaucoma, cells and a flare were noted. A diagnosis of secondary glaucoma was made, and mydriatics were prescribed. The subsequent rise in pressure was controlled with Diamox for one month. When I next saw the patient, the angle was completely and permanently closed, the pupil fixed at six mm., and the coefficient of outflow 0. Fortunately, the filtering procedure proved successful.

In acute narrow-angle glaucoma, a scratch or ab externo incision is easier to perform than a keratome incision. The incision should be started two mm. from the limbus, and beveled toward the base of the iris. Chandler[2] recommends suturing the corneal incision to facilitate prompt formation of the anterior chamber, and one must agree that this is a sound procedure.

In acute narrow-angle glaucoma, an iridectomy—peripheral or complete—is the operation of choice. The amount of iris removed will depend upon the preference of the surgeon. In older patients, a complete iridectomy may improve the vision (if there is marked central nuclear sclerosis) as well as facilitate delivery of the lens at a subsequent date. However, the pupil in these cases usually is miotic, and one has little difficulty in performing a peripheral iridectomy if this is the procedure of choice.

In interval narrow-angle glaucoma, or when performing a prophylactic iridectomy, one should use miotics prior to the retrobulbar injection, or omit a retrobulbar injection. One is likely to forget that blocking of the ciliary ganglion may cause wide dilatation of the pupil—which makes a peripheral

iridectomy difficult, if not impossible.

Damage to the lens may occur while making the incision, especially if a keratome is used. This may be evident immediately, or not until a few days postoperatively. Should the damage be extensive, the lens may swell, necessitating linear extraction. Lens damage may also occur from injury to the epithelium by the iris forceps, or tip of the anterior chamber irrigator. This may not be noticed unless looked for with a slitlamp. It may be slowly progressive, or remain stationary. The best prevention is to avoid entering the anterior chamber with any instrument, unless absolutely necessary. Toothless iris forceps are recommended.

Delayed formation of the anterior chamber predisposes to the formation of peripheral anterior synechias and the development of chronic congestive glaucoma. This is best prevented by tight closure of the wound, and reformation of the chamber by the injection of air through a preplaced knife needle tract in the cornea.

Chronic narrow-angle glaucoma

In cases that fall in this category, an operation usually is performed when there is first evidence of lack of control of tension with miotics. Visual function may not show deterioration, but a rising base pressure and decreasing facility of outflow usually are evidence that peripheral anterior synechias may be forming.

In early cases, a peripheral iridectomy may suffice to control the tension, with or without the postoperative use of miotics.[3] Advanced cases require a filtering procedure, and the complications of this procedure will be discussed later.

Malignant glaucoma

This dreaded complication occurs in both chronic congestive and chronic noncongestive glaucoma. Fortunately, it is not frequently encountered. It is seen in eyes with an extremely shallow chamber, in which there appears to be a forward displacement of the lens-iris diaphragm. The tension usually is elevated preoperatively regardless of the medication which has been given. Unfortunately, one cannot always predict when a malignant course may occur. One can only agree with Tamler and Maumenee[4] that in eyes with advanced iris-block glaucoma—which do not respond to miotics, and in which the anterior chamber is shallow—lens extraction as a primary procedure is probably indicated.

Once the diagnosis of malignant glaucoma is made, the surgeon must have the fortitude to remove the lens, even if it is clear. Shaffer[5] and Chandler[6] both agree that even if this is accomplished, the anterior chamber will remain shallow and tension high—unless the hyaloid face is ruptured and vitreous is lost or appears in the anterior chamber. Though usually this is a dreaded complication, in this instance it is the only feature that will save the eye. This does not necessarily follow if lens extraction is done as a primary procedure. Hence the importance of selection of cases in which this is indicated.

Filtering procedures

A filtering operation usually is planned for a rising base pressure in chronic congestive glaucoma and in chronic simple glaucoma, when there is evidence of loss of function. I do not propose to discuss the pros and cons of operation in chronic wide angle (simple) glaucoma, except to emphasize that there is no such thing as a "normal" intraocular pressure. Each patient has a critical pressure above which he loses function, and this may be 25, 35, or even 45 mm. Hg (Schiøtz). One should never operate on a patient with wide-angle glaucoma solely on the basis of his intraocular pressure.

An iridencleisis may be performed in many ways, each surgeon having his own preferences. The conjunctival flap should be large, and care should be taken not to buttonhole the flap. Should a buttonhole occur, it should be closed with a suture, and the scleral incision should be placed as

far away from the hole as possible. All bleeding should be controlled with pressure, and the minimal amount of cautery used at the expected site of the filtration area. Scheie[7] has recently advocated the use of the cautery on the lips of the scleral wound, as an aid in the formation of a cystoid scar. The incision in the sclera must be wide enough to permit the introduction of the iris forceps, and not too far posterior so that the ciliary processes will prolapse. A sclerectomy or hinging of the flap will depend upon the preference of the surgeon.

On opening the chamber, a few drops of aqueous may escape, the iris and lens appear to move forward, and the eyeball feel hard. This may or may not indicate a malignant postoperative course. Diamox, 500 mg. intravenously, may help alleviate the situation. Should the incision be enlarged, ciliary body and lens may present in the wound. Toothless iris forceps should be gently introduced and the iris withdrawn, the sphincter slit down to the base, and both pillars incarcerated in the edges of the incision. In my experience, there are too many unknown factors to determine whether two-pillar iridencleisis is better than one-pillar iridencleisis. As a general rule, I include a sclerectomy after the preparation of the scleral incision if the base pressure is 40 mm. Hg or more (Schiøtz).

After an iridencleisis, one seldom is worried about a shallow or absent anterior chamber. One may have a marked hyphema from external or iris bleeding. Should it cause a secondary glaucoma, a mild cycloplegic should be used, and also Diamox, if the intraocular pressure is uncomfortably high. The cycloplegic is used to prevent synechia. Seldom is it necessary to evacuate the clot from the anterior chamber.

A quiet iridocyclitis is not an unusual complication following iridencleisis. It is important to keep the pupil mobile. Hence, homatropine or neosynephrine should be used postoperatively, as well as local corticosteroids.

A cystoid cicatrix or bleb may be visible early; there may be only a diffuse edema of the conjunctiva; or there may be no external evidence of filtration. There may be adequate control of the pressure no matter which of the three conditions exist. The patient may require adjunctive medication for normalization of the intraocular pressure. Though the presence or absence of a bleb may or may not signify control, in my experience if—in a primary uncomplicated procedure—a bleb does not form, it is unlikely to form on subsequent filtration procedures.

One of the disadvantages of an iridencleisis is the occasional development of an updrawn pupil. This may make it difficult for the patient to read, and may complicate the extraction of a cataract should this become necessary at a later date.

Trephination

There are many ophthalmologists who prefer the trephining procedure when a filtering operation is required. Others reserve it for selected cases of open-angle glaucoma, when the base pressure is high, or as a secondary procedure if an iridencleisis has failed.

The disadvantages of the trephining procedure are:

1. It is technically more difficult to perform than an iridencleisis.

2. It frequently results in a shallow chamber postoperatively, and the lens may come in contact with the cornea.

3. A large cystoid bleb may form, which predisposes to (a) hypotony, (b) secondary infection, and (c) variable changes in the refractive error.

4. A rather rapid progression of preexisting lens opacities.

In performing the operation, it is essential that an adequate conjunctival flap be prepared, that it be dissected down to and include the corneal limbus. All bleeding should be controlled without use of the cautery if possible.

It is easier to perform this operation if the eye is firm. One should attempt to have the

pressure at about 30 mm. Hg. The trephine should be sharp, and should be 1.5 or 2.0 mm. in diameter. Ideally, when the trephine is removed, the scleral button—including all layers of the cornea and sclera—should pop up, hinged in only one small segment, with a knuckle of iris presenting in the opening. Should the iris not present, it may be difficult to perform the iridectomy. The opening usually is too narrow to permit the use of iris forceps. Sometimes suction with an eyedropper will prolapse the iris. Should this not be possible, the incision may have to be enlarged with scissors to permit the introduction of iris forceps.

Following the iridectomy—be it peripheral or complete—ciliary processes may appear in the opening. If the eyeball is not hard, and there is no obvious forward displacement of the lens iris diaphragm, they may be excised, taking precautions not to pull any more processes into the opening. The anterior chamber should then be filled with air, preferably injecting enough to balloon out the airtight conjunctival flap.

Occasional vitreous may appear in the wound. If there has been an anterior separation of the vitreous body, and fluid vitreous presents, no great difficulties may ensue. The presence of formed vitreous is a serious omen. Though I have not experienced this complication, in the few cases I have seen in which this has occurred, the results have been uniformly poor. It probably occurs as a result of a posteriorly placed trephine opening in an eye with forward displacement of the lens iris diaphragm, in which there is also a marked increase in the posterior chamber pressure. About the only treatment is excision of the vitreous, if it is formed, tight closure of the conjunctival flap, and the injection of air (as noted above) if the eyeball is not hard.

Damage to the lens may occur as an early or late complication.[8] Early clouding or swelling of the lens usually signifies damage by the trephine at the time of surgery. It is a serious complication that can be prevented by meticulous surgery, and the use of a guard on the trephine. Late opacification of the lens may be due to mild trauma to the lens capsule or, in the case of a nonexistent anterior chamber, to contact of the lens with the cornea. When the latter condition exists, and is associated with a choroidal detachment, the subchoroidal fluid should be evacuated, and the chamber filled with air. Removal of the lens at a later date may be necessary to improve vision, but seldom is required to overcome a secondary glaucoma caused by a swollen lens, unless it was severely damaged at the time of surgery.

Progression of lens opacities, or their fairly rapid development, is also seen following trephine surgery, when no complicating factors can be found. It usually occurs in the eyes which have been carrying a fairly high base pressure, and which have been rendered slightly hypotensive by surgery. It is probably caused by changes in the metabolism, secondary to marked reduction in pressure.

As following an iridencleisis one may not find any cystoid scar, one may have diffuse edema of the conjunctiva, or one may have a large filtering bleb. Absence of a cystoid scar does not always signify failure. DeVoe[9] reports successful control of the glaucoma despite no visible filtration bleb in 31 out of 43 eyes. The most successful results, so far as the patient and the surgeon are concerned, are those with diffuse pitting edema of the conjunctiva, and adequate control of the tension. Large cystoid scars with loculated transparent areas frequently are mechanically annoying to the patient. The normal blink reflex by massage of the bleb may create several diopters of astigmatism, causing marked blurring of the vision. Probably the most serious complication is the development of a fulminating secondary infection. With only a thin layer of cells protecting the interior of the eye from external ocular infections, it can be seen how pathogenic organisms can penetrate readily.

Rupture of a filtering cicatrix may occur. This usually is followed by reduction in vis-

ion, due to loss of the anterior chamber; and may even result in an acute hypotony with retinal edema and/or papilledema. Excision of the bleb and closure of the wound may lead to a return of the raised intraocular pressure. One can usually close the dehiscence by preparing a bridge flap of conjunctiva about six mm. wide from above the upper extremity of the bleb. The flap should be free in the center, so that it can be brought over the bleb, and held in place with two sutures placed at the limbus at the 9:30- and 2:30-o'clock positions. It will gradually retract, but the cystoid bleb is well protected if it is covered with this thick layer of conjunctiva.

Sympathetic ophthalmia is a dreaded complication of any intraocular surgery. Though one would suspect it might occur most frequently following an iridencleisis—since the iris is incarcerated in the wound—there are very few statistics proving this point. The incidence of sympathetic ophthalmia in all glaucoma surgery is probably not as high as following cataract surgery, or penetrating wounds of the eye.

Discussion

An attempt has been made to discuss the most frequent complications that may follow surgical procedures for primary glaucoma. As in any type of surgery, complications may occur, and they are not always the result of poor surgical technique. At times, they may be the result of errors of judgement, that is, a basal iridectomy may not be sufficient in a patient with early chronic congestive glaucoma. In chronic open-angle glaucoma, we are operating to relieve the increased intraocular pressure, with little knowledge of why it is elevated.

There are also some patients who, for no apparent reason, do poorly following surgery. They have delayed formation of the chamber, their conjunctiva heals firmly with no evidence of external filtration, they develop lens opacities more quickly than one would expect, and so forth.

Probably no other type of ophthalmic surgery requires such careful surgical judgement—especially in patients with open-angle glaucoma. However, if the indications for surgery are evident, that is, an acute attack of glaucoma, or a rising base pressure with loss of function, one should not procrastinate, but should proceed with the necessary surgery. The surgeon should use those techniques which he himself feels capable of performing, and which have proven to be satisfactory in the past.

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her evidence would not lead us to expect a

tained cells and turbid aqueous. The left eye

STEROID PROPHYLAXIS IN SYMPATHETIC OPHTHALMIA*

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Since the recognition of adrenal corticosteroid therapy as the first really successful treatment for sympathetic ophthalmia, there has been a great deal of speculation on the efficacy of these agents for prophylaxis. It has seemed to many that steroid treatment of potentially sympathogenic perforating injuries had sufficient promise for routine adoption. Woods[1] stated that he usually advised steroid therapy in potentially sympathogenic injuries in the hope that it would help to prevent the disease, and this attitude seems to be rather widespread. Newell[2] has recently stated, editorially ". . . routine administration of ACTH prevents the development of sensitivity to uveal pigment which may well predispose to sympathetic ophthalmia." It is the purpose of this paper to inquire into that point of view and present some evidence against it.

In a symposium on the uses and abuses of steroid therapy in 1955, I said,[3] "There is, however, no evidence to date that steroids have any prophylactic value against sympathetic disease." This rather negative statement was based on the lack of statistically sound evidence of its prophylactic value. Such evidence would be very difficult to come by.

Although many perforating ocular injuries throughout the world have had steroid therapy and have failed to develop sympathetic disease, can this be taken as evidence of cause and effect? Many eyes that have not had steroid treatment have also failed to develop the disease. How large a series of treated cases without a single occurrence of the disease would constitute sound statistical proof? This question evades an accurate answer.

The exact likelihood of sympathetic disease in the given series would have to be known and the types of injury admitted to the series rather rigidly defined. As an approximation we could take the usually accepted range of incidence of approximately two percent[4] of severe perforating injuries and accept for statistical significance the common figure of less than five-percent chance occurrence. The number of cases to make a series without the disease significant could then be calculated by binomial expansion as more than 148 cases. If we adopt the more rigorous criterion of less than one-percent chance occurrence, the size of the necessary series becomes 228. Using a standard binomial confidence limit table[5] we find the sizes of the necessary series of cases for less than five-percent and one-percent error, respectively, to be 180 and 267. No matter how we juggle the statistics it would seem that a series of a couple of hundred or more prophylactically treated cases without incidence of the disease should be had before any sort of claim for prevention could be made. I am unaware of even any such series, much less a properly designed experiment with adequate controls.

The amount, type, and duration of prophylactic treatment would also have to be specified. How much would be enough and for how long? Any logical, nonempirical answer to these questions would have to be based on a knowledge of the etiology of the disease—something we do not have.

If prevention should be based on a suppression of sensitization, there is at least some analogy by which we may be guided.

Loveless[6] has shown in man that "sensitizing antibodies, which are elaborated spontaneously by allergic individuals following specific contact, continued to be present in the blood serum in the same concentrations as before hormonal therapy." Although she was not dealing with sympathetic ophthalmia, if we are to consider this disease, in whole or in part, as a sensitization phenomenon,

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her evidence would not lead us to expect a prophylactic effect from steroids. If we do not postulate prophylaxis on a sensitization: inhibiting basis but on some still more obscure mechanism which might be blocked by steroids, are the risks, not to mention the inconveniences, of the side-effects justified in order to prevent something which has a 98-percent chance of not happening anyway?

On a purely empirical basis, using for prophylaxis that steroid therapy which is known to be of therapeutic value once the disease has set in, the demonstration of effectiveness of the program rests on the nonoccurrence of the disease in a series of cases larger than any yet reported, all of the type that could have developed sympathetic disease had they not had prophylactic steroid treatment. No such convincing series can be found in the literature. The occurrence of even one case of sympathetic disease after such prophylaxis would tend to overbalance an entire such series. One such case is here reported.

Report of case

D. D., an eight-year-old healthy white boy, suddenly perforated his right eye with a pen-knife while whittling. There was a through-and-through wound of the cornea and adjacent sclera, and prolapse of iris and possibly a small amount of ciliary tissue. The perforation was promptly and neatly repaired by direct suturing with excision of all prolapsed tissue by his local ophthalmic surgeon.

He was placed on intensive "prophylactic" steroid therapy with prednisone and also large doses of antibiotics. For a period of six weeks he seemed to do well. The injured eye had relatively little inflammatory reaction and fairly good light projection in spite of an opaque lens and some hypotension. The left eye remained entirely normal in every respect with normal visual acuity. The antimicrobial drugs were stopped and the corticosteroids slowly withdrawn. Four days thereafter he complained of difficulty reading. His ophthalmologist saw him on the next day and asked me to take over management of the case.

At the time of my examination two days after the onset of blurred reading vision and three days after the mother had noted "slight redness" of the left eye, the right vision was light perception, the left 5/200. The right eye was injected and soft with the scar of a perforating wound of the cornea and the pupil closed. The anterior chamber contained cells and turbid aqueous. The left eye showed moderate circumcorneal injection, photophobia, a "felted" iris, small pupil, and early posterior synechias. There were greasy deposits on the back of the cornea, cells and increased turbidity in the aqueous, and generally hazy media. Fundus detail was obscured. Tension felt normal. Diagnosis of severe, early sympathetic ophthalmia was made.

He was hospitalized and given 40 units of corticotropin intravenously over the next eight hours. Intensive topical atropine and phenylephrine were started, as well as topical hydrocortisone. For the next six days intravenous drip corticotropin was continued eight out of each 24 hours. He was then switched to 30 units of zinc corticotropin gel twice a day intramuscularly and the usual systemic precautions maintained. Topical atropine, phenylephrine, and hydrocortisone were continued. Eighteen days after admission he was discharged on 50 units of the zinc gel daily and topical atropine and hydrocortisone.

During the hospital stay both eyes had slowly become quiet. The injured right eye which was never enucleated became free from cellular reaction but failed to regain useful vision or normal tension. The sympathizing left eye maintained normal tension. The synechias broke and the pupil dilated. The iris slowly regained its normal texture, the cells in the aqueous disappeared, the corneal deposits diminished, and the aqueous flare became progressively fainter. Acuity improved from 5/200 on admission to 20/40 on discharge. The media cleared until the fundus could be well seen. There was some edema about the disc and posterior pole.

Over the next month intramuscular corticotropin was slowly withdrawn as was atropine. In spite of fluid and sodium restriction and potassium supplement there was considerable water retention and "mooning" of the face with slight hirsutism and acneform skin eruption. All of these side-effects were reversed after the systemic hormone had been discontinued. It was never perfectly clear whether the edema noted in the fundus was on an inflammatory or fluid-retention basis. In any event, over the next six weeks on topical hydrocortisone alone the fundus cleared and vision returned to 20/20 in the left eye. The right continued at light perception only.

For the next four months he was kept under close observation. Both eyes remained quiet and the left vision held at 20/20 on topical hydrocortisone twice daily and the use once a month of atropine to assure and test freedom of the pupil. For the next four months he was maintained on one drop of hydrocortisone daily in each eye. For the past three months his eyes have remained quiet with light perception in the right and 20/20 in the left on one drop twice a week.

This then represents a case of clear-cut sympathetic ophthalmia which developed in spite of six weeks of intensive prophylactic

steroid therapy. Furthermore, the subsequent response of the disease to therapeutic application of steroids shows that there was no peculiar lack of steroid sensitivity in this patient or this disease. It would seem to indicate rather strongly that steroid "prophylaxis" against sympathetic ophthalmia is not effective.

Many hundreds of cases of "successful" steroid treatment will be required to counterbalance the evidence of this one case statistically. No amount of statistical manipulation will ever gainsay the fact, as shown in this case, that sympathetic disease can ensue in spite of six weeks of steroid prophylaxis.

Would a longer course of prophylactic treatment have been of any greater preventive value? That question is, now at least, impossible to answer.

Would the boy have been better off if no steroids had been given unless the disease had occurred. Certainly he would have been no worse off!

Could the "prophylactic" steroids by suppressing the natural bodily defense mechanisms actually have favored the development of the disease? There is no evidence to support this hypothesis either.

There is a rather distant analogy in the evidence on the effects of steroids in diminishing ocular tissue resistance in tuberculosis.[7] Although the clinical and histologic features of ocular tuberculosis and sympathetic ophthalmia have much in common we are not justified in drawing too close a parallel.

It would seem then that the case for adrenocorticosteroid prophylaxis against sympathetic ophthalmia is not substantiated. The arguments for it rest on shaky ground. The statistical proof of its efficacy is lacking. Definite evidence of its failure is presented. The suggestion that it may actually predispose to the disease is backed by argument at least as tenuous.

In the absence of proof of its value, in the presence of proof of its failure, under the cloud of suspicion (however undocumented) of its harmfulness, would we not be better advised to avoid "prophylactic" steroid therapy of penetrating ocular injuries? Would not careful observation of the potentially sympathogenic injury and the state of its fellow eye so that adequate treatment could be promptly instituted be safer? Might not prolonged misguided and ill-conceived "prophylaxis" so suppress without truly conquering the disease as to result in delay in its recognition and energetic treatment to the ultimate detriment of the patient?

Summary

The use of adrenocorticosteroids following penetrating ocular injuries for the purpose of preventing sympathetic ophthalmia is discussed. Lack of proof of its value is shown and a case demonstrating its failure is cited. It is suggested that such treatment of penetrating wounds be withheld in the best interests of the patient.

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A METHOD OF GRADING AND RECORDING*

THE RETINAL CHANGES IN ESSENTIAL HYPERTENSION

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In the course of a long-term study of the natural history of essential hypertension,[1, 2] a semiquantitative method has been developed which permits the retinal changes in individual patients to be graded and recorded in a uniform and reproducible manner at various stages in the evolution of the disease. The method has proved to be of value in studies of the correlation between the retinal changes and various clinical and laboratory manifestations of hypertensive vascular disease. It has also been used in evaluating the effect of antihypertensive therapy on the retinal vascular abnormalities which occur in hypertensive patients.

The criteria used in grading the severity of various retinal abnormalities are based on modifications of several previous systems which have been devised to serve the same purpose.[3–5] Since we have tried to grade each component of hypertensive retinal disease separately, our method resembles the system recommended by the American Ophthalmological Society's Committee on "Classification of hypertensive disease of the retina,"[3] rather than that of Keith, Wagener, and Barker[6] which merely assigns a single, overall grade to the retinal findings in each patient.

Since our main objective was to record the vascular changes in the fundus, especially in their early stages, with as high a degree of reproducibility as possible, the advantages to be gained by the use of special graticules or by means of retinal photography were given very serious consideration. In our experience, however, the outlines of the vessels in retinal photographs are not sufficiently distinct to permit one to detect many important, qualitative changes in the appearance of the arterioles or to make accurate measurements of arteriolar caliber. Moreover, the time required to take a large enough number of pictures to permit a comprehensive view of the fundus to be reconstructed is too great to be practicable for our purpose. The need for an unusual degree of co-operation and steadiness on the part of the patient, which is the chief obstacle to the successful use of a graticule, is also an important disadvantage of retinal photography, especially in dealing with seriously ill patients who are confined to bed.

It is possible that the many improvements which are currently being made in retinal photographic equipment may cause us to change our opinion, but at the present time we believe that the principal value of retinal photographs is as an adjunct to visual examination of the fundus, particularly as an aid in the accurate localization of specific points of reference such as arteriovenous crossings. In this investigation, therefore, we have relied on careful ophthalmoscopic examination of the fundus through the dilated pupil as the basis for our grading of the retinal changes, but in order to ensure that all examinations are carried out in a uniform manner, a worksheet has been devised to serve as a guide to the examiner and to provide a

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permanent record of the results of the examination.

Description of the worksheet

The worksheet used to record the data is designed to be filled in by a secretary or technician as the ophthalmologist dictates his findings with the aid of a simple code. The use of the abbreviations of which the code is composed permits a detailed examination of the average hypertensive fundus to be recorded in about 20 minutes, and prevents the patient's anxiety from being aroused by overhearing words such as hemorrhage and arteriosclerosis whose unfavorable connotations are widely appreciated.

When the worksheet is used as an aid to the precise documentation of changes which have occurred between one examination and the next, the secretary can fulfill a most important function by calling major discrepancies between the two records to the ophthalmologist's attention as soon as he has completed his examination. For example, if an area of localized arteriolar narrowing which was reported on one occasion is not mentioned during a subsequent examination, the secretary should ask the ophthalmologist to recheck the area and to make a definite statement to the effect that the finding in question is no longer present.

The following description of the worksheet is illustrated by Figure 1 which is a reproduction of the record of an ophthalmoscopic examination performed on a 40-year-old woman with early Keith-Wagener grade IV retinopathy. The center panel of the sheet lists the more important types of abnormalities which may occur in the retina in essential hypertension, namely, generalized arteriolar narrowing (GN) which is estimated by means of the arteriovenous ratio (A/V), increased or decreased arteriolar tortuosity (AT), abnormalities of the light reflex of the arterioles (LR), localized arteriolar narrowing (LN), engorgement of the venules (VE), tortuosity of the venules (VT), arteriovenous crossing phenomena (AVC), hemorrhages (H), cotton-wool patches (CWP), edema residues (ER), edema (E), papilledema (P), and retinal vascular accidents (RVA). The term retinal vascular accident refers to occlusions of the central retinal artery or its branches, or of the central retinal vein or its tributaries.

The two side panels of the worksheet provide space for recording the findings in the right and left eyes respectively. Each side panel is divided into four major columns, one for each quadrant, and each major column is further subdivided to provide adequate space for recording the principal abnormalities of the corresponding quadrant. When more space is required, additional entries may be made in the blank space at the bottom of the sheet. The order in which the major columns are arranged corresponds to the sequence in which the quadrants are examined, namely, upper temporal, lower temporal, lower nasal, and upper nasal. At the end of the quadrant-by-quadrant examination the macula and the disc are examined, and the findings are recorded in the sections provided at the bottom of the sheet.

Estimates of length and distance are made in terms of the average diameter of the disc (DD), and direction is indicated by clockface bearings with respect to the center of the disc. Bearings are given to the nearest half-hour, but in order to save space the half-hour is indicated by an apostrophe; thus, a bearing midway between the 10- and 11-o'clock position would be recorded as 10′. The location of any point in the retina can be specified by means of its clockface bearing and its distance from the disc margin; this distance is expressed in "disc diameters from the disc" (DD-D). On this notation, the disc margin is at 0 and the center of the disc is at $-\frac{1}{2}$ DD-D.

Generalized arteriolar narrowing (GN)

The top section of the worksheet is devoted to an estimate of the caliber of the arterioles in terms of the arteriovenous ratio (A/V). The shortcomings of the A/V

NAME Mrs. M.K. DATE 11/18/53 OPHTHALMOSCOPIC EXAM

AGE 40 BP 180/120 (lying) RX Nov. Br. (s.c.) 10 days EXAMINER J.V.V.N.

RIGHT EYE

UPPER T.	LOWER T.	LOWER N.	UPPER N.
A A1 A2 B	A	A B	UTQ A1 A
11 UN - 9'	8	5' 4	- 2'
- - 6 -	-	8 5	7 -
- - 2 1	2	2 1	2 1
2 - 0-2 -	1F	2 1-2	2 -
A2 A2	A A1		UTQ A1
1 1	1 1	0	1
8 8	8-9 9		8
0 0	0 ?		?
1/7 1/7	1/3 1/2		>
1 1/2 2 1/2	1/2 2		2
A A1 A2	A B	A B	UTQ A1 A
0 UN 0	1 0	0 0	0 0
2 - 2	2 1	2 2	2 2
2 2 1	-	2	1
11 10 11		4	2'
1 1/2 2 1/2 3		1/2	1 1/2
1	1 1 1	0	0
1/2	1/10 1/8 1/8		
f	l l l		
10'	6 7 7'		
3/4	1/16 0 1/8		
0	1 1	0	1
	1/4 1/6		1/8
	6' 8		12'
	2 3 1/2		3/4
About 30 / mm		0	2 1
8-10 o'clock			1' 1'
0 - 1 DD - D			1 2 1/2
1	1	0	0
0	0	0	0

ARTERIOLE	UPPER T.	LOWER T.	LOWER N.	UPPER N.
BEARING	1 2'	4 - -	7'	9' 10 11 11'
A/V (V=10)	- -	- 6 8	-	- - - -
TORTUOSITY	2 2	- 2 2	2	1 1 1 1
REFLEX	2 2	- 1 1	1-2	1 - - -
ARTERIOLE	A A	A1 A2		A
LN-NUMBER	1 1	3 n	0	1
A/A EX 10	8 9	9 7-9		7
TYPE	0 0	0 0		0
LENGTH	1/7 1	- -		1/3
DD-D	1 1/2 2	- -		1/8
VENULE	A	A A1 A2	A B	A B
ENGORGEMENT	1	0 0 0	0 0	0 0
TORTUOSITY	2	- 2 2	2 2	2 2
AVC - GRADE	1	2 2	2 1	-
BEARING	1'	4' 5	6' 8	
DD-D	1 1/2	2 3	1 2 1/2	
H - NUMBER	0	3	0	2
SIZE		1/16		1/8
TYPE		n		n
BEARING		5		10'
DD-D		2 1/2		3
CWP-NUMBER	1	0	0	0
SIZE	1/2			
BEARING	2			
DD-D	2 1/2			
ER - NUMBER	About 15, same	0		0
BEARING	area as on			
DD-D	right			
EDEMA	1	1	0	0
RVA	0	0	0	0

MISCELLANEOUS

MACULA: H 0 CWP 0 E 1 ER 0 STAR 0

DISC - SURFACE: COLOR sl. blush CUP visible

MARGIN: Blurred except from 1-5 o'clock

EDEMA: trace - mainly on nasal half

MEDIA OK REFRACTION OK ACUITY - R 20/30 L 20/20 MEDIA OK REFRACTION OK

SUMMARY: A/V-.67 LN: Q 6 Nas A/A-.77 LR 1.7 AVC 1.6 RVA 0 H 9 CWP 4 E 1 ER 45 STAR 0 P 1

No significant change since last exam. 2 weeks ago. A small H in UTQ has faded out.

Fig. 1 (Evelyn and Nicholls). *Example of completed worksheet.*

Abbreviations: A = arteriole; A/A = ratio of width of narrowed portion of arteriole to width of adjacent normal portion; A/V = ratio of width of normal portion of arteriole to width of corresponding portion of venule; AVC = arteriovenous crossing phenomena; BP = blood pressure; CWP = cotton-wool patch; DD = disc diameter; DD-D = distance in disc diameters measured from disc margin; d = diopter; E = edema; ER = edema residue; F = focal; f = flame-shaped; H = hemorrhage; L = left; LN = localized narrowing; LR = light reflex; l = linear; N = nasal; No. = number; n = numerous; o = organic; P = papilledema; p = punctate; Q = quadrant (UTQ, LTQ, LNQ, UNQ = upper temporal, lower temporal, lower nasal, upper nasal quadrant); R = right; RVA = retinal vascular accident; Rx = therapy; r = round; T = temporal; t = tonic; tr = trace; V = venule; > = distal portion of arteriole.

ratio as an index of arteriolar caliber are fully appreciated, but no other reference base is available unless measurements are made on retinal photographs or by means of an ophthalmoscope fitted with a special graticule. Dilatation of the reference venule will result in an underestimate of the A/V ratio; this cannot be avoided entirely, but an estimate of the degree of engorgement of the venules is part of the regular examination, and this can be used to make an approximate correction. In our experience, however, errors due to engorgement of the reference venule are relatively unimportant compared to those which may be caused by the common practice of estimating the A/V ratio in quadrants in which a single venule drains all the blood which reaches the area through two, three, or four arterioles.[5, 7] This appears to be the situation, for example, in the illustration of grade 2 generalized arteriolar narrowing which is given in Figure 3 in the article by Wagener, Clay, and Gipner.[3]

In order to ensure that A/V ratios are estimated only in those quadrants where the arterioles and venules are equal in number and have similar patterns of branching, the first step in the examination of each quadrant is to record the number of arterioles (line 1 in the worksheet) and the number of venules (line 12).

The arterioles which cross the disc margin in a given quadrant (excluding those that are too small to be identified with certainty as arterioles) are designated by the letters of the alphabet, beginning with the arteriole closest to the proximal edge of the quadrant and following the standard sequence of examination, namely, counterclockwise in the right fundus and clockwise in the left. The same rule is followed in assigning letters to the venules.

The clockface bearing of the point at which each arteriole crosses the disc margin is given on line 2. This makes it possible to identify a given arteriole in the reports of two different ophthalmologists, even though different letters may have been assigned to it as a result of one examiner's having included in his list of lettered arterioles a small vessel which the other had decided to ignore.

If the examiner feels that the distribution of an arteriole is sufficiently similar to that of the corresponding venule to justify comparison, the numerator of the A/V ratio is entered on line 3 in the appropriate column, the denominator, corresponding to the size of the venule, always being taken as 10.

The A/V ratio is usually estimated at a distance of about one disc diameter from the margin of the disc. Therefore, when the arteriole and the venule divide into their two primary branches shortly after crossing the disc margin, a separate estimate of the A/V ratio is recorded for each branch. In such instances, for example, in the upper temporal quadrant of the right fundus in Figure 1, the primary branches of arteriole A are designated A_1 and A_2, the subscript 1 being assigned to the branch on the side closest to the proximal margin of the quadrant. It will be noted, in this same quadrant, that an A/V ratio has been recorded for the branches of arteriole A even though there is an arteriole B for which there is no corresponding venule; the examiner is at liberty to do this if he feels that arteriole B is so small relative to arteriole A that the amount of blood carried by it is negligible.

Apart from the problem of asymmetric distribution of the blood vessels, the most serious source of difficulty in estimating the A/V ratio is the presence in the arteriole of numerous areas of localized narrowing. When there are only one or two such areas the ratio is estimated at a point where the arteriole looks most nearly normal, but when the whole length of the arteriole has an irregular outline due to multiple areas of organic narrowing of varying degrees, the A/V ratio can no longer be considered as an index of generalized narrowing in the ordinary sense. However, even in such extreme cases, it is useful to record the A/V ratio estimated on the basis of the least narrowed portion of the arteriole.

The upper temporal quadrant of the right eye in Figure 1 also illustrates a common difficulty in applying the rules for assigning identifying letters to the arterioles. It often occurs, as in the case of arteriole A_1 in this quadrant, that a major portion of the blood supply of one quadrant is provided by a branch of the main arteriole of an adjacent quadrant. When this occurs, the branch is included in the list of arterioles in both quadrants, but the actual findings are recorded in the quadrant to which the arteriole is distributed (in this case the upper nasal) rather than that in which it arises.

Arteriolar tortuosity (AT)

In view of the wide range of arteriolar tortuosity which is encountered in normal fundi, this item is not regarded as of major significance in the evaluation of hypertensive disease of the retina although it is recorded as a matter of interest. The numerical grade assigned to this item is based entirely on the examiner's mental image of the tortuosity of a normal retinal arteriole; this is arbitrarily defined as tortuosity grade 2. Moderate degrees of decreased or increased tortuosity are graded 1 and 3, respectively, while grade 0 is reserved for arterioles which are almost completely straight and grade 4 for the most extreme degrees of tortuosity. In evaluating the significance of decreased arteriolar tortuosity the number of arterioles which supply blood to the quadrant is a most important factor; for example, in the upper nasal quadrant of the left eye in Figure 1 there are four small arterioles each of which is straight enough to justify a tortuosity grade of 1.

Arteriolar light reflex (LR)

In the earlier versions of the worksheet provision was made for the grading of the light reflex and the opacity of the arteriolar wall as separate items. Experience has shown, however, that arteriolar opacity is one of the factors which is taken into consideration in grading the light reflex and that it also contributes an important element to the arteriovenous crossing phenomena which are graded under AVC. We have felt, therefore, that no real purpose is served by grading opacity as a separate item but, if desired, opacity of the vessel wall or pallor of the blood column may be graded in the "miscellaneous" section.

According to our criteria, grade 1 implies that the light reflex is brighter and/or wider than normal but that the blood column on either side of the reflex stripe has a normal appearance. Grade 2 corresponds approximately to the "copper wire arteriole" in which a light reflex of increased width and brilliance is combined with paling of the blood column due to a decrease in the transparency of the vessel wall. Grade 3 corresponds to the "silver-wire arteriole" in which the light reflex is extremely brilliant and is widened to the point where the blood column can barely be seen, and the arteriolar wall may be visible as a separate structure. Grade 4 is reserved for arterioles which appear as white, fibrous cords, the blood stream no longer being visible even though the lumen is not completely obliterated. A subnormal light reflex may be graded −1, but when the reflex is not visible merely because the arteriole is too small, the symbol − should be used.

Since it is quite common for the light reflex to vary in different parts of a single arteriole, it is often necessary to record a double grade such as 1-2 or 2-3, or even 0-2 as in the upper temporal arteriole of the right eye in Figure 1. When the areas of increased light reflex are confined to short isolated stretches of the arteriole the designation "F" (focal) is used, the grade being recorded as 1F or 2F as the case may be. Such areas often coincide with the sites of localized narrowing of the arteriole; this is referred to as "focal sclerosis" by the Committee on Classification.[3]

The phenomenon of periarteriolar sheathing is not included in the grading of abnormalities of the light reflex but is described in the "miscellaneous" section.

Localized arteriolar narrowing (LN)

When there are only a few well-demarcated areas of arteriolar narrowing, each area should be identified as fully as possible by: (1) entering on line 6 the code designation of the arteriole or arteriolar branch in which it occurs, (2) recording on line 8 the degree of narrowing in terms of the width of the narrowed portion relative to that of the normal arteriole proximal to it, the width of the normal arteriole being assigned a value of 10 (A/A ratio), (3) expressing an opinion on line 9 regarding the type of narrowing, whether tonic (t) or organic (o), (4) stating on line 10 the length of the narrowed portion in DD, using the symbol > to indicate that the narrowing involves the entire distal portion of the arteriole, and (5) giving an estimate on line 11 of the straight-line distance between the margin of the disc and the beginning of the localized narrowing (DD-D).

It is by no means easy to differentiate tonic arteriolar constriction (often referred to as spasm) from narrowing due to sclerotic changes in the wall of the arteriole. Nevertheless, it is considered worthwhile to try to make this distinction, especially in a clinical investigative project which has as one of its objectives the study of the reversibility of localized arteriolar narrowing, either spontaneously or in response to therapy. The principal criterion by means of which sclerotic narrowing can be identified is the presence in the narrowed region of fine irregularities of the blood column, especially when there is an accentuation of the light reflex in the same area. Narrowing due to increased arteriolar tone is suspected when the blood column is smoothly and symmetrically narrowed, and when the light reflex in the narrowed area is normal or reduced, and especially when other signs of retinal arteriolosclerosis, such as arteriovenous crossing phenomena, are not prominent.

When there are numerous localized narrowings on a single arteriole, and especially when, as is usually the case, they are of the sclerotic type, it is both unnecessary and impracticable to try to record each area separately. In such instances it is sufficient to record the number of narrowed areas in each arteriole and to indicate the A/A ratios of the areas of maximum and minimum narrowing; this technique has been used, for example, in the lower temporal quadrant of the left eye in Figure 1. When, as was the case in arteriole A_2 in this quadrant, one narrowed area merges imperceptibly into the next so that it is impossible to count the number of individual narrowings, the number is recorded as n (numerous).

When long stretches of an arteriole are narrowed either in a uniform or in an irregular manner, the use of the A/A ratio as an index of the degree of narrowing is unsatisfactory because there is no adjacent area of normal arteriole for comparison except at the point where the narrowing begins. It may even be difficult in the extreme case to decide whether one is dealing with relatively slight focal narrowings superimposed on a moderate degree of generalized narrowing, or with a confluent series of localized narrowings of various lengths and degrees in the absence of generalized narrowing.

Most of the rules which we have followed in the grading of localized arteriolar narrowing as well as those used in grading generalized narrowing are based on the assumption that the least narrowed portion of an arteriole can be assumed to be the most nearly normal. If, as has been claimed by Leishman,[10] it is a common occurrence for portions of an arteriole which have become fibrosed to dilate passively in the presence of hypertension, it may be necessary to reconsider our policy in respect to the selection of "normal" sections of narrowed arterioles.

Engorgement of venules (VE)

There is no satisfactory, objective basis for the grading of generalized engorgement of the venules, but an attempt is made to follow a rough, 4-grade system in which grade 1 is the minimum degree of engorge-

ment which can be detected with certainty, while grade 4 is the most extreme degree such as is seen when a major retinal vein is occluded. The main value of the grading of the engorgement of venules is that it serves to call attention to the possibility that the degree of arteriolar narrowing and the severity of the arteriovenous crossing changes will be overestimated as a result. Localized engorgement of a venule distal to a grade 4 arteriovenous crossing should be recorded in the same way although it should be differentiated from generalized engorgement. However, the alternate dilatation and narrowing of retinal venules which may occur in diabetic patients is a manifestation of generalized venous sclerosis and should not be recorded under engorgement.

It will be noted in this paragraph and in Figure 1 that we have departed from the terminology of the Committee on Classification[3] by using the term "venule" instead of "vein" to refer to the ophthalmoscopically visible branches of the central retinal vein. Since the committee has recommended the use of the term "arteriole" in referring to the branches of the central retinal artery, it seems more consistent to use the term "venule" for the corresponding venous channels.

Tortuosity of venules (VT)

This item is graded on the same basis as arteriolar tortuosity, the normal curvature of the venules being described as grade 2.

Arteriovenous crossing phenomena (AVC)

Each crossing in which the arteriole overlies the venule is identified in terms of its clockface bearing and its distance from the disc margin, and the degree of abnormality is graded on the usual 0-4 scale. Grade 1 implies that there is no more than slight compression and/or displacement of the venule by the arteriole. In grade 2 the depression and displacement of the underlying venule are quite definite, and the increased opacity of the wall of the arteriole is sufficient to reduce the visibility of the blood within the venule on either side of the point where it is crossed by the blood column of the arteriole. In grade 3 there is definite kinking of the venule so that the angle which it makes with the arteriole approaches a right angle. The area of obscuration of the column of blood in the venule is much wider than the diameter of the arteriole, and there may be slight engorgement of the distal portion of the venule. The cardinal feature of AVC grade 4 is the marked engorgement of the venule which occurs distal to the crossing because the flow of blood through the venule is very seriously obstructed.

Hemorrhages (H), cotton-wool patches (CWP), and edema residues (ER)

We have adopted the terminology recommended by the Committee on Classification[3] for the description of the localized retinal lesions of hypertensive retinopathy. The term "cotton-wool patch" is applied to the fluffy white areas which are sometimes referred to as "soft exudates." The term "edema residues," which corresponds to the "hard exudates" or "waxy exudates" of previous terminology, is used to describe all types of discrete, white spots which resemble edema residues, even though there may be no evidence, in a particular instance, that the appearance of the lesions was preceded by ophthalmoscopically demonstrable retinal edema.

When the number of hemorrhages in a given quadrant is small, a record is made of the size, type, and location of each one. Size refers to the maximum dimension expressed in fractions of a disc diameter, but when the hemorrhages are very small the abbreviation p (for punctate) is used. The type or shape of each hemorrhage is recorded as linear (l), flame-shaped (f), or round (r). When several small hemorrhages occur in a small cluster the whole group may be recorded in the same column, as has been done, for example, in the lower temporal quadrant of the left fundus in Figure 1. When numerous

hemorrhages of various sizes are scattered throughout the quadrant, only the approximate number of hemorrhages and the size of the largest and smallest are recorded.

The other types of localized retinal lesions (CWP and ER) are recorded in similar fashion, but when the edema residues are arranged in the form of a star figure they are recorded in the special section of the worksheet which is devoted to the macula.

Edema (E)

The four grades used in describing the degree of retinal edema are little more than substitutes for the common descriptive terms slight, moderate, marked, and extreme. Thus, grade 1 is a barely discernible degree of edema, which may be indicated by irregular highlights at the posterior pole, grade 2 gives the appearance of a definite grayish haze in the peripapillary or macular areas, while grade 3 is sufficient to obscure the finer branches of the retinal vessels and those portions of the larger vessels which lie in the deeper layers of the retina. Grade 4 edema, which is very rarely seen in the fundi of hypertensive patients, is extensive enough to produce localized areas of detachment of the retina.

Retinal vascular accidents (RVA)

In this section of the worksheet a note is made of the occurrence of occlusions of the central retinal artery or its branches or of the central retinal vein or its tributaries. It is important that hemorrhages caused by occlusion of a small retinal venule should be labelled correctly as such, since, as Wagener, Clay, and Gipner[3] have pointed out, the hemorrhagic and edematous lesions resulting from organic closure of retinal vessels should not be classified under the heading of hypertensive retinopathy.

Abnormalities of the macula

Space is provided in this section to record the presence at the posterior pole of hemorrhages, cotton-wool patches, edema, and edema residues which might be expected to affect the acuity of central vision. The size and shape of a partial or complete star figure should be recorded in such a way that it will be possible to decide on a subsequent examination whether the lesion is advancing or receding. For this and similar descriptive purposes, schematic diagrams of the two fundi are printed on the back of the worksheet to permit a rough sketch of the situation to be made. Other abnormalities of the macula such as pigmentary degeneration also are recorded in this section.

Abnormalities of the optic disc

The entries in this section of the worksheet are intended to ensure the recording of the earliest signs of papilledema as well as to indicate the degree of elevation of the disc when definite papilledema is present. Separate entries are made regarding the color of the disc (pallor, hyperemia), the appearance of the physiologic cup, and the sharpness or otherwise of the disc margin. When the disc margin is blurred the clockface bearings of the blurred section are recorded and an opinion is given as to whether the blurring is within the limits of normal or could be explained on some other basis such as refractive error.

Refractive media and visual acuity

The next line on the worksheet permits a record to be made of any abnormalities of the refractive media which may impair the visibility of the fundus. These include not only opacities in the lens and vitreous but also major refractive errors which may introduce artefacts into the evaluation of blurring of the disc margin or localized arteriolar narrowing. When hypertensive retinopathy is present a record should also be made of the patient's visual acuity (with correction) so that any alterations which occur can be correlated with changes in the degree of involvement of the macula.

Summary

Finally, an attempt is made to summarize all the abnormalities observed during the examination in a series of numerical entries

which can be used as a basis for correlating the retinal findings with other clinical and laboratory data. The numerical summary is also of value in documenting the progress of the retinal vascular disease in patients who have been subjected to repeated ophthalmoscopic examinations at various stages in the evolution of essential hypertension.

The items included in the summary and the way in which the overall numerical assessments are made are as follows:

1. *A/V ratio.* The figure recorded here is the average of all the ratios recorded on line 3. In the patient whose data are shown in Figure 1, the average numerator of the A/V ratio is 6.7 ($6+8+5+7+6+8$ divided by 6), therefore the A/V ratio is recorded as 0.67.

2. *LN.* Three separate entries are required to summarize the data on localized arteriolar narrowing, namely, the number of quadrants in both fundi in which one or more arterioles are affected (Q), the number of individual areas of localized narrowing observed (No.), and the mean A/A ratio calculated from the values recorded for the most markedly narrowed arteriole in each quadrant (A/A). When there are several poorly demarcated areas of localized narrowing in several of the arterioles it may be impossible to make an accurate estimate of the total number of areas and the symbol n (numerous) may have to be entered under No. However, when the localized narrowings are sharply defined and relatively few in number, an accurate enumeration may be made without difficulty and will provide a useful basis for comparing the findings on successive examinations.

3. *LR, AVC,* and *E* are summarized in terms of the mean of all the individual grades recorded on the corresponding lines of the worksheet. It is realized that there are many valid objections to the practice of calculating the arithmetic mean of a series of arbitrarily defined numerical grades in which the differences between successive grades are not necessarily equal. Nevertheless, the use of such data has proved to be of real value in giving an early indication of occurrence of changes which subsequent observation shows to have been significant.

4. *H, CWP* and *ER* are recorded as the number of each type of lesion in both fundi, the code letter n being used when the lesions are so widespread as to be countable only with great difficulty. Edema residues are often widely scattered and numerous enough to require the use of the abbreviation n, but when a macular star is present, this fact is recorded separately under the heading "star."

5. *P.* Papilledema is summarized by recording the number of diopters of elevation on the worse side, the abbreviation tr (trace) being used to indicate the presence of definite edema of the nerve head without measurable elevation.

It is fully appreciated that a much less detailed summary of the ophthalmoscopic findings is quite adequate for most practical purposes. In ordinary clinical work the single, over-all Keith-Wagener grade is by far the most widely used notation, while the system described by Page and Corcoran[4] includes separate grades for each of five parameters, namely, generalized arteriolar constriction, arteriolar hyalinization (which includes our LR, LN, and AVC), hemorrhages, "exudates," and papilledema. However, the detailed summary provided by our worksheet has the advantage of presenting almost all the information which can be derived from examination of the fundus in a form which lends itself readily to tabular presentation, as in Table 2. Numerical data of this sort are essential for adequate follow-up of patients in a long-term study, and the use of a standardized system of grading and recording is of particular value when the examinations are performed by more than one ophthalmologist.

Reproducibility of the grading

Nicholls, Turnbull, and Evelyn[8] have reported observations on the A/V ratios in 200 normotensive individuals and in 100 hypertensive patients of whom 33 were examined

independently by two ophthalmologists (J. N. and W. T.). In these patients, there were 145 arterioles which were considered suitable for grading by both observers, and in 41 percent of these the two estimates of the A/V ratio were identical, while the difference was 0.1 in 47 percent and 0.2 or more in 12 percent. The mean A/V ratios calculated from the two sets of data on the 33 hypertensive patients were 0.64 and 0.66, respectively, and the coefficient of linear correlation was 0.86. When the comparison was made in terms of the average A/V ratio for all gradable arterioles in both fundi of each patient, rather than on the basis of the grading of individual arterioles, the ratios obtained by the two observers differed by more than 0.15 in only one case. These results were obtained by excluding all patients (about 11 percent of those examined) in whom gradable arterioles were found in less than three of the eight quadrants; this was arbitrarily taken as the minimum number of gradable quadrants which justified the calculation of a mean A/V ratio. On the basis of our present criteria, gradable vessel pairs were found in about 70 percent of the temporal quadrants and in about 50 percent of the nasal quadrants examined.

When each of these observers examined a separate series of 100 normotensive patients representing all decades from the first to the eighth, the mean A/V ratio was 0.75 in one series and 0.77 in the other. The results of these two experiments indicate that the criteria used in estimating the A/V ratio, though highly subjective, can be applied with a relatively small margin of error.

Unfortunately, our results, which are summarized in Table 1 together with those obtained by Bjork[9] on the basis of graticule measurements, show that the differences between the A/V ratios of normotensives, mild hypertensives, and severe hypertensives (excluding those with papilledema) are disappointingly small. It seems fair to conclude, therefore, that the accurate estimation of the degree of generalized arteriolar narrowing (as opposed to localized narrowing), while of interest from the research standpoint, is not likely to be of much practical value as an aid to diagnosis or prognosis in the great majority of hypertensive patients. It must be emphasized, however, that our failure to find a consistent reduction in the caliber of the major retinal arterioles in hypertensive patients should not be interpreted as casting doubt on the existence of a significant diminution in the caliber of the precapillary arterioles where most of the peripheral vascular resistance is located. Relatively small changes in vessels of this size, which are

TABLE 1

COMPARISON OF OUR DATA ON ARTERIOLAR CALIBER WITH RESULTS OF DR. S. BJORK

Type of Patient	K-W Grade	DBP	Nicholls et al.[8]				Bjork[9]			
			No. of cases	A/V Ratio			No. of cases	A/V Ratio		
				Min.	Max.	Mean		Min.	Max.	Mean
Normotensive	0	< 90	100	0.60	0.95	0.75*				
			100	0.56	0.99	0.77†				
			200	0.56	0.99	0.76	59	0 60	1.07	0.82
Hypertensive	0–2	<110	39	0.45	0.83	0.65	45	0.50	0.95	0.77
Hypertensive	0–2	>110	40	0.42	0.87	0.67	38	0.56	0.99	0.77
Hypertensive	3		10	0.38	0.81	0.62	16	0.56	1.04	0.77
Hypertensive	4		5	0.33	0.69	0.47	13	0.32	0.97	0.61

* Patients examined by J.N.
† Patients examined by W.T.
Abbreviations: K-W = Keith-Wagener retinal grading; DBP = diastolic blood pressure; min. = minimum; max. = maximum.

too small to permit estimates of caliber to be made by means of ophthalmoscopic examination, may have highly significant hemodynamic consequences.

Localized arteriolar narrowing, although not detectable by ophthalmoscopic examination in all cases of hypertension, is a much more reliable sign of hypertensive vascular disease than generalized narrowing because the incidence of localized narrowing of the retinal arterioles is very low in normotensive individuals. For example, in a study of 103 normotensive controls, Leatham[8] found occasional instances where a single retinal arteriole showed slight localized narrowing, but there was no case in which such narrowing was observed in two or more retinal arterioles. Our own data show that localized narrowing is very rare in the younger age groups, although it is present in about three percent of patients over 60 years of age. Another important advantage of localized retinal arteriolar narrowing as a sign of hypertension is the fact that it can be identified with much greater certainty than is possible in the case of generalized narrowing.

The reproducibility of our gradings of localized arteriolar narrowing must be considered from two points of view, namely, the degree of narrowing and the localization of the narrowed areas. Except in those cases in which there are multiple confluent areas of narrowing, and in those where the arterioles are partly obscured by edema, the reproducibility of independent estimates of the A/A ratio is at least as good as that of estimates of the A/V ratio. When the length of the narrowed area was less than one DD, differences of 0.2 or more between the A/A ratios reported by two independent examiners occurred in only 11 instances out of a total of 124 areas examined.

The errors in estimating the lengths of areas of localized narrowing and their distance from the disc were often quite large, but this was found to be due almost entirely to difficulty in defining the points at which an area of gradual tapering of the blood column commenced and ended. It was because no simple method could be devised to eliminate this source of error that the system finally adopted for summarizing the degree of localized narrowing has been based primarily on the number of quadrants involved and the maximum degree of narrowing in each quadrant, the number of narrowed areas being recorded only when they are discrete and clearly defined. However, even when dealing with well-demarcated areas of grade 2 or 3 narrowing in which there was no difficulty in deciding where each narrowed portion began and ended, the discrepancy between independent estimates of the distance from the disc margin was often as great as 0.25 disc diameter at a distance of one disc diameter, increasing to 0.5 disc diameter or more at a distance of two to three disc diameters. In investigating the problem of the reversibility of localized arteriolar narrowing, therefore, no significance was attached to the apparent disappearance of an area of narrowing between one examination and the next, unless the arteriole was found to be of uniform caliber for a sufficient distance on either side of the site of the original narrowing to exclude the possibility that the initial area may have been incorrectly localized.

Reproducibility of the entries in other sections of the worksheet did not present any serious problems. In the grading of LR and AVC discrepancies of one grade between the estimates of independent observers occurred frequently; this is unavoidable whenever arbitrary numerical grades are assigned to a parameter which is capable of assuming all possible values intermediate between one grade and the next. There was, however, no evidence of systematic bias in any one direction in the estimates of five members of our group (two ophthalmologists and three internists) who have employed this system of grading during the past few years. Differences of two grades in the assessment of the same arteriole by different examiners were very rare indeed

because the difference between the criteria of grade 1 and grade 3, for example, is sufficiently clear-cut to eliminate any uncertainty as to which of these grades should be applied to a given arteriole. The chief difficulty in the evaluation of abnormalities of the light reflex and the arteriovenous crossings was not lack of reproducibility but lack of specificity for hypertension, since grade 1 and even grade 2 changes are by no means uncommon in normotensive subjects, especially in the older age group.

The error in recording the number of localized retinal lesions, such as hemorrhages and cotton-wool patches, can be reduced to almost any desired level provided enough time and care are taken. Fortunately, however, it is only when the number is relatively small (as in the case illustrated in Figure 1) that it is important to detect minor changes; therefore, it is usually sufficient to record the approximate number of lesions of each type in each quadrant when dealing with patients with widespread hemorrhages or extensive retinopathy.

Use of the worksheet in serial examinations on the same patient

During the past nine years this system of grading and recording the ophthalmoscopic findings has been used in over 300 hypertensive patients, many of whom have been examined on five or more occasions over a period of five years. These patients have also been studied intensively from the general clinical and laboratory points of view, in order to provide data for use in a study of the correlations between various manifestations of the hypertensive process. Although it is not our intention to discuss the clinical results in the present paper, a condensed tabular summary of the data on one of the patients who was followed for five years (table 2) is presented as an illustration of the use of the method to record the changes in the ophthalmoscopic findings which may occur in the evolution of hypertensive vascular disease.

Case report

This patient was selected for purposes of illustration, partly because she was followed from an early stage of the disease when the fundi were virtually normal until death, and partly because she is one of the few patients in our series in whom we have observed definite changes in the localized narrowings of retinal arterioles in the absence of special circumstances, such as toxemia of pregnancy or acute hypertensive retinopathy with papilledema.

Our first record of this patient was in August, 1948, when she was admitted to the Department of Gynecology for a minor complaint. At this time she was 36 years of age and her blood pressure was 160/98, but she had no cardiac or cerebral complaints and her fundi were not examined. When seen one year later for a recurrence of the gynecologic complaint, her blood pressure was markedly elevated (average of six casual readings 255/150) and the electrocardiogram showed grade 1 left ventricular hypertrophy, but she was still free of hypertensive symptoms and renal function as measured by the PSP test was perfectly normal. Our first detailed fundus examination, which was made at this time, was within normal limits except for one mild localized arteriolar narrowing in each of two quadrants and grade 1 abnormality at three of 11 arteriovenous crossings.

Two months later, in January, 1950, the general clinical situation and the results of the fundus examination were unchanged except for the fact that no localized arteriolar narrowings were recorded. Unfortunately, however, at this stage in the evolution of our system of examination the reproducibility of our results was not sufficient to permit us to be sure that the narrowed areas had, in fact, disappeared.

During the next few months there was a slight worsening of the electrocardiogram and a slight decrease in renal function and the patient began to have frequent episodes of focal cerebral ischemia which produced mild, transitory, sensory, and motor symptoms on the left side of the body; these attacks were of the type which is sometimes attributed to "cerebral vasospasm."

Fundus examination in October, 1950, showed widespread localized arteriolar narrowing, definite abnormalities of the light reflex and arteriovenous crossings, a few hemorrhages and cotton-wool patches, and slight but definite papilledema. After a three months' trial of the rice diet the cerebral symptoms continued to occur, but the retinopathy had cleared completely although there was no significant improvement in the retinal vessels, and the electrocardiogram and PSP test showed further deterioration.

Thoracolumbar sympathectomy was performed in March, 1951, but it resulted in only a moderate, temporary fall in the blood pressure taken in the lying position although there was severe orthostatic hypotension for several months. The patient was free of cerebral symptoms for about nine months following the operation, and there was a short-lived

TABLE 2

SUMMARY OF CLINICAL AND OPHTHALMOSCOPIC DATA ON MRS. E. B.

Date	Clinical and Laboratory Data					Therapy	Ophthalmoscopic Findings										
	Blood Pressure (mm. Hg)	Cardiac Symptoms	ECG (LVH)	Cerebral Symptoms	PSP: % in 30'		A/V	LN			LR	AVC	H	CWP	E	ER	P
								Q	No	A/A							
8/ 5/48	160/98	0		0													
9/15/49	240/160	0		0													
11/ 4/49	272/134	0	+	0	50.5		0.7	2	2	0.8	0	0.3	0	0	0	0	0
1/10/50	232/138	0	+	0	48.8		0.75	0	0	—	0	0.2	0	0	0	0	0
10/ 5/50	270/154	+	++	Frequent attacks of focal cerebral ischemia, July, 1950, to March 1951	45.3		0.75	7	10	0.65	1.0	0.9	3	2	0	0	tr
10/26/50	210/120					Rice diet											
1/10/51	242/124																
1/25/51	230/130	++	+++		42.0		0.7	5	6	0.6	1.4	0.6	0	0	0	0	0
3/ 1/51	250/148					Thoracolumbar sympathectomy							2	0	0	1	0
3/ 6/51	240/140																
3/22/51	170/115		++	No attacks March to December, 1951	46.3		0.75	2	2	0.65	1.4	1.1	1	0	0	1	0
12/ 5/51	200/115	++	+++		42.3		0.65	7	13	0.6	1.2	1.0	0	0	0	0	0
9/ 7/52	280/150	++		CVA gr. 3 with left hemiparesis													
9/ 9/52			+++		39.1		0.6	8	18	0.4	1.6	1.3	0	0	0	0	0
9/18/52																	
9/24/52	170/110					Hexamethonium	0.6	7	10	0.65	1.7	1.5	0	1	0	0	0
3/28/53	244/140	++	++++	Multiple small CVA's with mental deterioration													
10/28/53	260/160	++			36.3		0.6	7	13	0.7	1.9	1.3	0	1	0	0	0
1/10/54				Fatal cerebral hemorrhage													

Abbreviations: ECG = electrocardiogram; LVH = left ventricular hypertrophy; PSP = phenolsulfonphthalein test; CVA = cerebrovascular accident; other abbreviations as in legend to Figure 1.

improvement in the electrocardiogram and in the degree of localized retinal arteriolar narrowing.

In December, 1951, the attacks of focal cerebral ischemia recurred, and eventually, in September, 1952, there was a definitive cerebrovascular accident with left hemiparesis which took several weeks to clear. On this admission the most striking change in the fundus was a marked increase in the number and degree of localized arteriolar narrowings but there was also some evidence that the abnormalities of the light reflex and arteriovenous crossings had increased slightly.

When the ophthalmoscopic examination was repeated two weeks later (after the blood pressure had been reduced temporarily to nearly normal levels by hexamethonium injections), there was an unequivocal reduction in the number and degree of the localized arteriolar narrowings which resulted in a change in the mean A/A grade from 0.4 to 0.65.

Subsequently, the patient became refractory to the blood-pressure lowering effect of hexamethonium, the recurrent episodes of focal cerebral ischemia gradually gave rise to general mental deterioration (chronic hypertensive encephalopathy), and the slow decline of renal function continued. Eventually, the patient died of a massive cerebral hemorrhage four years and four months after the markedly elevated blood pressure was first observed.

The last complete ophthalmoscopic examination, which was performed two months before death, showed that the retinal vascular abnormalities had not increased significantly during the previous year. However, when all the data on this patient are examined in broad perspective, with adequate allowance for the imperfect reproducibility of the gradings, the predominant trend is a steady progression of the retinal vascular disease which seems to have been affected only slightly by therapy, even though treatment with the rice diet was followed by complete disappearance of the retinopathy.

Comment

The decrease in localized arteriolar narrowing after sympathectomy appears to have been genuine, but at that time (1951) we were still in the process of refining our method of recording, therefore it was not until the 1952 episode that we felt full confidence in our demonstration of the partial reversibility of the localized arteriolar narrowing in this patient. It should be emphasized, however, that the primary objective of our investigation was to document the progress of the disease from year to year throughout its course, therefore it was only in a small minority of our patients that examinations were repeated at short enough intervals to provide any data at all on the frequency with which localized arteriolar narrowing may be expected to disappear spontaneously or in response to treatment. Certainly, on the basis of the results of repeated annual examinations, the localized narrowings of the ophthalmoscopically visible arterioles in the great majority of our patients who were suffering from the ordinary varieties of chronic essential hypertension appeared to be constant in position and slowly, sometimes very slowly indeed, progressive.

Summary

1. A system of criteria has been devised whereby each of the ophthalmoscopically visible manifestations of hypertensive vascular disease may be assessed on a semi-quantitative basis. The method incorporates many of the features of several other systems which have been developed for the same purpose.

2. A worksheet is described which permits the data to be recorded in a manner which facilitates the correlation of the ophthalmoscopic findings with other clinical and laboratory manifestations of the disease.

3. Data are presented to indicate the reproducibility of the gradings which can be achieved when the same fundus is examined independently by two observers. In the case of generalized arteriolar narrowing as measured by the A/V ratio the margin of error, though quite small, is relatively large when compared with the magnitude of the difference between normotensives and hypertensives (in the absence of papilledema).

4. The use of the method is illustrated by a tabular protocol showing the changes which were observed in a patient who was examined repeatedly during a four-year period beginning soon after the onset of hypertension, and ending shortly before the patient's death.

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KERATOPLASTY FOR HERPETIC KERATITIS*

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Herpes simplex virus infection of the cornea continues to be one of the most important problems in the field of ophthalmology. In spite of the introduction of many new therapeutic agents in the past decade, none has yet been found to be effective in this disease.

With the advent of the broad spectrum antibiotics, it was thought at first that an effective agent for the herpes simplex virus had been found in aureomycin. Braley and Sanders,[1] in initial studies, reported that this drug favorably influenced the course of herpetic keratitis. Later, Braley and Alexander,[2] and MacKneson and Ormsby[3] reported that aureomycin had an inhibitory effect on this virus in vitro. Subsequently, however, clinical trial failed to substantiate these early favorable reports, and it is now generally agreed that none of the antibiotics has any influence on herpetic disease.

Cortisone and ACTH also were thought at first to have an important place in the treatment of herpetic keratitis. In all forms of stromal herpes, including disciform keratitis, the inflammatory reaction was suppressed when steroids were administered, and patients experienced symptomatic relief. Laboratory studies by Thygeson, Geller, and Schwartz,[4] and by Ormsby, Dempster, and van Rooyen,[5] conclusively showed that cortisone prolonged the acute phase of herpetic keratitis in rabbits, and caused perforation of the cornea in some instances. Clinical trial in humans subsequently showed that steroids had an unfavorable effect on the course of dendritic ulceration, and in some instances could activate a latent infection. It is now agreed by most authorities that steroids are to be avoided in all phases of the disease.

The tendency for herpetic keratitis to recur, often after an interval of months or years, warrants the conclusion that the virus lies latent in the cornea between attacks. The dendritic ulcer occurs in the epithelium and can be cured by cauterization and epithelial denudation. This treatment fails to prevent recurrent attacks, however, and it must be assumed that the virus lies latent in the corneal stroma. Treatment by corneal

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transplantation should therefore be of value by removing tissues harboring latent virus, and at the same time improving vision.

Keratoplasty technique in herpetic keratitis

Both lamellar and full-thickness grafts have been used by keratoplasty surgeons in the treatment of herpetic keratitis. When the corneal scar involves the deeper layers of the stroma and Descemet's membrane, full-thickness grafts are necessary if good vision is to result. Hogan[6] has shown, however, that when full-thickness grafts are used as a primary procedure in herpetic keratitis, clouding of the cornea due to antigen-antibody reaction is of frequent occurrence.

When the present program of corneal grafting was instituted at the University of Toronto in 1954, it was decided to carry out all keratoplasties on herpetic eyes by means of the total (10-mm.) lamellar method, and to perform full-thickness optical grafts only as a secondary procedure. To date, 25 eyes with herpetic keratitis have been operated upon by the lamellar technique, and in two of these eyes, secondary five mm. full-thickness grafts have been performed to give normal vision.

Radiation has not been used preoperatively, since most of the vessels could be removed by the dissection. Postoperatively, vascularization of the graft has not been a problem, and has been controlled to a large extent by the use of topical steroids.

In removing the host tissues, the 10-mm. Castroviejo trephine was set at a depth of 0.6 mm., and the corneal incision carried out by rotating the trephine with the fingers. The edge of the corneal lip was grasped in its healthiest portion with Saint-Martin forceps and the incision carried more deeply with a No. 15 Bard-Parker blade. By keeping the field absolutely dry, and by lifting the cornea upward with tension, the corneal stromal fibers could be seen to separate and assume a vertical striation. By peeling off these fibers at their base with the knife, a very deep dissection could be performed, close to Descemet's membrane.

Perforation during the course of this deep dissection occurred in four eyes with Descemetocoeles. The resultant lowering of intraocular pressure aided the placement of the graft, and did not appear to hinder the healing processes in any way. However, some stromal edema persisted for three to five weeks in the grafts in these cases, and some permanent deep scar was formed over the area of perforation.

All grafts were fixed by eight 6-0, edge-to-edge fine silk sutures. Healing was rapid in all herpetic corneas, and the sutures were removed in most instances between the seventh and 10th days. Atropine was applied with each dressing, and hydrocortisone ointment was started after the seventh postoperative day. After the removal of the sutures, the eye was left uncovered and the hydrocortisone ointment was applied four times daily by the nursing staff.

Following discharge from hospital, the patient used hyoscine drops morning and night in the eye until all signs of iritis had subsided, and hydrocortisone was used topically for another four to eight weeks. As a result of this treatment no graft reactions occurred, and vascularization of the bed, and of the graft itself, has been minimal. In the the first six cases, however, when hydrocortisone was not used postoperatively because of the fear that herpetic infection might be activated, vascularization in the bed was extensive, and two grafts developed antigen-antibody reactions with subsequent clouding.

Results

In this series, all cases have been surgically successful. Healing has been rapid and postoperative complications have been minimal.

Six eyes have been operated upon because of the danger of perforation of descemetoceles. One of these eyes perforated following admission of the patient to hospital, and a bubble of air was seen in the anterior

chamber. In four eyes, rupture occurred during the dissection. In all six eyes, healing of the graft was satisfactory, but residual edema persisted for some weeks, and is still present in one graft five months after operation.

In 10 eyes, surgery was performed to terminate a long period of active keratitis which had failed to respond to the usual methods of treatment. These patients experienced relief of their symptoms within 48 hours after operation, and did not exhibit any undue postoperative reaction in the graft. The remaining eight eyes were operated upon during the quiescent phase of the disease.

The visual results were gratifying in all eyes in which the scar tissue did not extend to Descemet's membrane. In those patients in whom only one eye had been involved in the disease process, we have done no subsequent full-thickness grafts. Patients have usually been satisfied with the visual result and with freedom from symptoms. In two patients who had suffered from bilateral herpes, and had had bilateral lamellar grafts, subsequent six-mm. full-thickness grafts have been performed on the eye with the poorer vision. These grafts have remained clear.

Recurrence of herpetic infection has not appeared in any of the grafted eyes, in spite of the postoperative use of hydrocortisone. One patient operated upon in August, 1954, to cure an active infection of four months' duration, had 20/20 vision in the operated eye. In August, 1957, he returned with a dendritic ulcer on the other eye. This was the initial infection in this eye and developed during an attack of lobar pneumonia. The ulcer was terminated by iodine cauterization. The previously grafted eye did not show any signs of activity.

Discussion

The lamellar technique would appear to offer many advantages over full-thickness procedures in the treatment of herpetic keratitis. Although the proper performance of a 10-mm. lamellar graft, carried to the deep stromal level, requires much surgical skill and practice, there is less hazard involved in the operation, and healing is more rapid.

Even though the final visual result with a lamellar graft may not be equal to that of a successful full-thickness graft, most patients seem satisfied with the result, and postoperative complications are rare.

While many ophthalmologists would hesitate to recommend full-thickness grafts in vascularized corneas, and relatively few surgeons have the necessary training to perform them, most would agree that after some opportunity to practice on animal or eye-bank eyes, the lamellar technique could be performed with the same hope of success as cataract extraction.

It has been our experience that steroids have greatly reduced the postoperative reaction in these eyes. Since we have not had any recurrence of herpetic infection as a result of this procedure, it seems likely that all latent virus has been removed.

In our hands, the 10-mm. lamellar graft is no more difficult to perform than the smaller seven-mm. lamellar grafts which we have been doing in eyes with superficial corneal scars and in corneal dystrophies. The proximity of the limbal tissues in large grafts may be a factor in the rapid healing which we have experienced.

Summary and Conclusions

1. At the present time no therapeutic agent is available which will eliminate latent herpes simplex virus from infected corneal tissues.

2. Total lamellar (10 mm.) deep transplantation removes invading blood vessels and scar tissue from all but the deepest stromal layers, and probably removes all the latent virus.

3. Twenty-five total lamellar grafts in eyes with severe recurrent herpetic keratitis have resulted in relief of symptoms, and in varying degrees of improved vision.

4. Secondary full-thickness grafts (six mm.) in two of these eyes developed no

surgical complications and have remained clear.

5. No re-infections with simplex virus have yet occurred in any of the grafted eyes.

6. The use of corticosteroids postoperatively has not resulted in the exacerbation of infection, has reduced postoperative reaction, and has contributed to a better visual result.

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EPITHELIZATION OF THE ANTERIOR SEGMENT

After cataract extractions

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Epithelial invasion of the anterior chamber following cataract operations appears to be increasing, as shown by a further study of enucleated eyes in the Eno Laboratory of the New York Eye and Ear Infirmary.

Out of the 31 specimens sent to the laboratory from within the hospital and outside sources for the two years following a joint report[1] before the 1955 meeting of the American Ophthalmological Society, five of these exhibited epithelization.

Microscopic evidence of extracapsular operative technique was present in only one globe. This follows the trend as shown in the last five years of the joint report[1] on the causes of enucleation. The report extended for a quarter of a century and included 333 specimens. Approximately 25 percent of the "postcataract" eyes were affected in the latter period. It was during this time that the effects of intracapsular technique became evident.

It is not the purpose of these observations to indict the intracapsular technique as predisposing to epithelial downgrowths but to call attention to these complications and guard against them, if possible.

In a recent presentation, Maumenee[2] stated that 14.3 percent of the eyes enucleated after cataract extractions showed the complication of epithelial inclusions. No reference was made as to the type of operation employed but the incidence of one out of every seven enucleated eyes affected by this complication is startling.

Although many reasons have been given for downgrowths, none has been accepted as final. The loss of vitreous at the time of operation followed by poor union of the wound may prove to be the most important factors. Collapse of the anterior chamber, prolapse of the iris, buckling of the operative wound, and invasion of the suture tract have been noted. Which factor will prove to be the major underlying cause remains to be determined.

TABLE 1

PRIMARY DIAGNOSES OF 333 SPECIMENS AFTER CATARACT EXTRACTIONS FOR 25-YEAR PERIOD AND 31 FOR A SUBSEQUENT TWO-YEAR PERIOD

	25-Year Period	Two Subsequent Years 1955–1956
Uveitis with secondary glaucoma	151	17
Epithelial downgrowths	60	5
Uveitis	54	4
Sympathetic ophthalmitis	20	0
Endophthalmitis	19	1
Expulsive hemorrhage	12	3
Intraocular tumor	11	0
Endophthalmitis phacoanaphylactica	5	1
Panophthalmitis	1	0

In the early report it was noted that 60 of the 333 specimens showed invasion of the anterior chamber by epithelium. Only three percent of the eyes were so affected during the first 12 years of the period but during the last five years 25 percent were involved. The two subsequent years show the same trend, with five of the 31 specimens invaded and all operated by the intracapsular or attempted intracapsular method.

A comparison is shown in Table 1.

CASE REPORTS

CASE 1

A typical case is exemplified by an intracapsular operation with the loss of vitreous in a man, aged 72 years, at the infirmary in 1939. The section was made with a Graefe knife, a conjunctival suture was inserted, and the incision was enlarged with the scissors. An attempt to deliver the lens in capsule was followed by the escape of a small amount of vitreous. The extraction was completed with the loupe without breaking the capsule. Additional conjunctival sutures were added and tied. The pillars of the iris were replaced and a conventional dressing was applied to both eyes. The vision, two months after operation, was 20/70 with correction in the operated eye. By the fifth postoperative month the eye was red, the tension increased, and the cornea "steamy." With the development of secondary glaucoma, hypopyon ulcer, and suspected invasion of the anterior chamber by epithelium, the eye was enucleated nine months after the operation. The microscopic examination revealed an epithelial lining of the anterior chamber (fig. 1) with hypopyon ulcer and secondary glaucoma.

CASE 2

A second example of an epithelial ingrowth with cyst formation (fig. 2) occurred in a man, aged 46 years, operated in 1952. The cyst was treated by evacuation and injection of iodine solution two years later without success. This procedure was followed by cyclo-electrolysis and later by cyclodiathermy. Finally, an iridectomy and cyclodialysis were performed in 1955 before the enucleation. The pathologic diagnosis revealed cystic epithelization

Fig. 1 (Payne). Typical epithelization of the anterior chamber reflected on the iris.

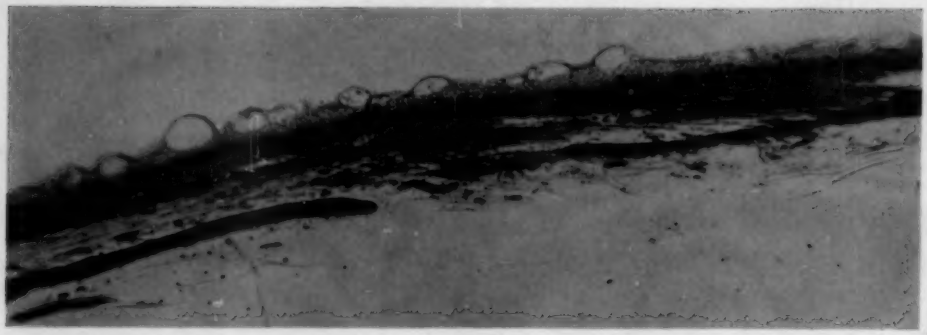

Fig. 2 (Payne). Epithelization of atrophic iris undergoing cystic change.

of the anterior chamber extending into the sclera, secondary glaucoma, and vitreous hemorrhage.

Comment

The clinical course of epithelial downgrowths following cataract extraction is essentially the same in all cases. The eye remains inflamed and seldom blanches completely. Usually, there is a haze and steaminess of the cornea in the region of the incision. The vision is diminished and cannot be improved. The intraocular pressure begins to rise and careful examination with magnifying aids shows a slowly advancing, grayish apron of tissue on the posterior surface of the cornea. Unless the process stops, it is reflected on the anterior and later the posterior surfaces of the iris and may form cystic extensions. Unfortunately, no satisfactory treatment has been devised and most patients suffer until the enucleation is performed. The pathologic diagnosis is made without difficulty by the obvious presence of epithelium in the anterior chamber.

The above observations confirm the findings in five representative laboratories in the United States in which 11 to 21 percent of the eyes enucleated after cataract extraction showed epithelization of the anterior chamber. Since the average is approximately 15 percent, epithelial downgrowths become major complications following cataract surgery.

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THE MANAGEMENT OF SECOND-DECADE CATARACTS

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A review of the recent ophthalmologic literature reveals only an occasional remark concerning this interesting group of cases, yet it seems safe to assume that these problems arise more frequently than the scattered mention might suggest. Having treated a fair number of these cases ourselves, we thought it might be profitable to present a small series, in order to share this experience with others. The present report is particularly appropriate for this issue of The Journal, since we had the singular good

fortune of having both Sir Stewart Duke-Elder and Dr. Derrick Vail as consultants on one of the cases to be presented.

There is considerable disagreement among authorities over the advisability of performing surgery on this group of cataracts. It is hoped that the case reports to be presented may shed some light on the questions which make the decision usually so difficult. We have had experience with several cases in which surgery was not performed, and three in which it was. An illustrative case history will be presented from each group.

Case reports

Case 1

C. P. During the second year of the patient's life it was first noted that the right eye was becoming periodically inflamed. Because of a moderate amount of mucopurulent discharge despite the slight circumcorneal injection, a diagnosis of conjunctivitis was made, and no treatment was recommended. There were, however, periods of quite intense inflammation, and there appeared to be some photophobia. When the patient was nearly three years old, the eyes were formally examined for the first time. An office examination did not seem feasible, so, despite the handicaps, all examinations were performed in the home. The past history was essentially negative. There had been no serious general illnesses. No other eye abnormalities had been noted. There was no history of venereal disease. The family history was not remarkable except for scattered instances of intermarriage. The examination revealed the following:

Vision. The patient was too young for accurate testing. In the right eye light perception was certain but good projection was uncertain. The vision in the left eye appeared normal.

External. The general appearance and position of the eyes were normal. The lids were not remarkable except for a moderate lagophthalmos, O.U. The palpebral conjunctivas were uninflamed. There was definite, but moderate, ciliary injection on the right. The corneas were 14 mm. in diameter, and the anterior chambers were very deep. However, no corneal cloudiness was noted. Discharge was minimal. The pupil on the right was semidilated but reacted to light. There was a fairly dense, posterior, subcapsular lens opacity. The tactile tension was normal. The anterior segment of the left eye appeared entirely normal, and the lens was clear.

Fundi. Right eye. Through small pupils, the media were very hazy. The disc could be made out only with difficulty, and no other fundus details were visible.

Left eye. The media were clear. The disc, macula, and vessels were normal, although there was incomplete myelination of the nerve fibers on the disc accounting for an indefinite outline of the nervehead.

For lack of an accurate diagnosis, no treatment was instituted. The picture remained much the same through the next six months. It was at this time, following his appearance as guest of honor at the annual meeting of the American Academy of Ophthalmology and Otolaryngology, that Sir Stewart Duke-Elder visited St. Louis, along with several other members of the American Board of Ophthalmology. These consultants agreed one evening to conduct a joint examination of this baffling eye.

The examination was complicated by the patient's unbelievably bad co-operation and the marked photophobia. No adequate examining table being available, the patient was examined on the floor, the consultants kneeling or lying prone as their various agilities would allow. We felt ourselves especially fortunate in having Sir Stewart Duke-Elder present, because of his interest and knowledge in the field of aqueous humor dynamics and intraocular fluid balance. Actually the most precarious problem during the examination was the balance of certain extraocular fluids of quite low aqueous content.

The anterior segments were essentially as previously described. The corneas were clear, still measuring 14 mm., but for the first time the intraocular pressure felt elevated on the right. The media of the right eye were exceedingly cloudy but the consensus was that there was evidence of a posterior, as well as an anterior, uveitis. The left eye was uninflamed but presented a poorly defined, roughly linear, posterior, subcapsular opacity. However, in this eye, despite the clearer media, no evidence of uveitis could be found.

There was a unanimous opinion that the right eye should be left undisturbed for fear that an operation might stir up the inflammation and since the vision in the left eye was obviously still good. A survey was contemplated but, in the absence of Dr. A. C. Woods, it was voted down as having little probability of revealing anything significant. It was felt that the interpretation of the usual barrage of skin tests, blood tests, and X-ray films would have been particularly difficult in this case, and the expense would have been exorbitant. No nonspecific treatment was recommended, intravenous typhoid just then going out of fashion and steroids not being readily available at this early date.

The condition remained stationary for approximately eight years, the cataract in the left eye progressing very slowly. The right eye suffered several exacerbations; finally the pupil became fixed to light, and there was apparently no light perception. Quite suddenly when the patient had reached the age of 11 years, the left eye became inflamed, presenting the same picture as that seen earlier on the right. A low-grade, smoldering uveitis led, within a matter of months, to the production of a quite dense cataract, diminishing vision to

bare light perception. Despite the marked visual impairment, it was decided that surgical intervention was still contraindicated, on the grounds that there probably was considerable retinal damage, and the hazards of surgery were too great. There has been no cause to regret this decision. As long as the patient is confined to his own home, he manages very well and, except for bumping against an occasional piece of furniture which has been moved from its accustomed place, one would hardly be aware of the visual disability.

The first case is presented in considerable detail, both because of the interest of the case and because of the uniform opinion of several experts, including Duke-Elder and Vail, that surgery should not be performed.

The second case, representative of so many, is presented in less detail, but sufficient to illustrate the points we want to make:

CASE 2

Cheryl B., a 13-year-old female, presented with bilateral, dense, cortical cataracts, apparently coming on over a period of approximately two years. The family were tremendously anxious that surgery be attempted, so, despite our lack of enthusiasm, it was decided to operate on the right eye.

For a change, the surgery was relatively uncomplicated. The conjunctiva was too thin to allow the use of a flap. A limbal groove was made, and three corneoscleral sutures were preplaced at widely separated intervals. The anterior chamber was entered with a keratome and the incision was widened with scissors. Following a peripheral iridectomy, the lens was grasped with Arruga forceps and delivered within its capsule, no great difficulty being encountered. The lens was huge, representing a large part of the ocular contents. There was no loss of vitreous but the large loss of volume, attributable simply to removal of the lens, made the eye so soft and so disturbed its normal contours, that the placing of the remaining 12 corneoscleral sutures became exceedingly difficult and one could not be sure of perfect apposition of the wound edges. However, the closure was good enough to allow water-tight filling of the anterior chamber with saline.

The preceding description does not tell the whole story, however. The operation was attended by a maximum of minor difficulties. It was two and a half hours in duration. No satisfactory position of the head was ever obtained. The ether cone kept sliding into the surgical field, and sterile conditions were almost impossible to maintain. The use of the electric razor was highly unsatisfactory and quantities of hair were continually appearing on the conjunctiva and in the anterior chamber. No adequate method of draping could be found, the opening in the eye sheet having a tendency to gravitate annoyingly to a position approximately over the right ear. The extremely awkward position necessitated by the unusual angle of the head forced the surgeon to perform the operation hunched over the operating table in a continually half-sitting, half-standing posture. Consequently he was completely exhausted at the end of the procedure, suffering a lame back and a crick in his neck for nearly a week thereafter. The effect on his disposition was incalculable.

Postoperative care was as usual very difficult. Co-operation was nil; arm splints of quite clever design could not prevent a constant pawing at the eye. A considerable vitreous haze persisted and the visual acuity seemed only slightly improved at best. The prescription of glasses was, of course, out of the question.

Besides the lack of real improvement, there seemed to be a noticeable psychologic change for the worse. Instead of docile acceptance of near blindness, the approach of strangers occasioned signs of apprehension, distrust, and antagonism in the patient. On occasions she was found to bare her teeth, growl, and even bark menacingly. It was regretfully concluded that she would probably have been happier if nothing had been done in the first place.

COMMENT

The reasons for failure are not immediately apparent. Probably a combination of factors enters into the picture. The surgery is difficult, and complications are the rule rather than the exception. However, as illustrated by the last of the two cases presented, even apparently perfect surgical results may end in functional failures. It can only be concluded that the marked hyperopia produced by removing the very strong, posteriorly placed lens from the eye of the dog, plus the impossibility of wearing a correcting lens, makes the visual acuity so low that it is probably very nearly comparable to that present preoperatively, notwithstanding the presence of a cataract. Moreover, with so few years ahead of them, most of these older animals seem to adjust remarkably well to their poor vision, and much of their apparent distress is associated with other manifestations of age.

In the first case cited, Chapper P., blindness occurred relatively early in life, and his adjustment was so complete that visitors were frequently unaware that he was blind. In our experience of three operated cases,

two were utter failures, and one, only a partial success. It is submitted that in the majority of instances, the chances of failure so outweigh the chances of any remarkable success that one may well be justified in leaving all but the exceptional case alone.

SUMMARY

Two sample case histories are presented illustrating opposite methods of handling cataracts occurring in the second decade. The first of these is especially interesting in that both Sir Stewart Duke-Elder and Dr. Derrick Vail were available for consultation.

It is concluded that, except for rare instances, surgical intervention is unwise and that adjustment to blindness in this age group is far easier than is generally realized.

100 North Euclid (8).

REFRACTION: SOME PRACTICAL SUGGESTIONS*

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It is a great pleasure to me that I have been considered as among the many friends of Sir Stewart Duke-Elder, and, as such, have been asked to contribute a paper to this testimonial number of THE AMERICAN JOURNAL OF OPHTHALMOLOGY, published in his honor upon the occasion of his 60th birthday. In seeking for a subject appropriate to the occasion, it seemed suitable to write something concerning the art of refraction, a subject upon which Sir Stewart has published a text that has become a classic.

As the title suggests, what is to be considered here will be some practical suggestions concerning refraction, rather than the optics and mathematics of the subject. An effort will be made to point out a few of the pitfalls which may preclude the attainment of the best results.

A difficult refraction tests not only all the technical skill and ingenuity of the refractionist, but also requires an understanding of the physical make-up of the patient, and the effect that general disease and ocular neuroses may have upon the ocular condition.

The peculiar and often startling changes of refraction in the diabetic are outstanding examples of the need for medical knowledge on the part of the examiner. A conspicuous instance is that of a patient who had been under my care for a number of years, who, upon returning for examination shortly after a satisfactory refraction, was found to require a reduction of one diopter from the glasses just prescribed. I suspected diabetes and questioned her concerning such a possibility. She felt certain that such could not possibly be the case, as she had been having monthly examinations of her renal function since an operation for the removal of one kidney a year previously. My next contact, three weeks later, was through her son, who, coming to the office about his own eyes, thanked me greatly for my intervention. Her blood sugar had been found to be 300 mg. per cc., but was now reduced to 125 mg. per cc. Shortly afterward she called herself, asking replacement of the one diopter previously removed. Then, in another three weeks, she was back again, peering at me across the room through the lower segments of her bifocals. At this time, she required an additional +4.25D. for good distant vision. The problem then arose as to what to do for her. Obviously, this great increase in hyperopia would not continue for any length of time. She demanded relief but to prescribe new bifocals of the required strength, and then others of lesser strength in two or

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three weeks, and so on, would be economically unsound. It was, therefore, decided to prescribe the necessary plus 4.25D. addition, both for near and far, in the form of clip-ons. These were reduced twice in the next six weeks, the measurements eventually returning to the original prescription.

Fundamentals of refraction

Retinoscopy is, without much doubt, the most favored method of refraction today. It is an objective procedure and, therefore, requires the least co-operation and intelligence from the patient. Since refraction is first learned in the clinic, where the average I.Q. is lower than that encountered in private practice, it is, as a rule, the method first mastered by the young ophthalmologist. Such examinations can be remarkably accurate but, in many instances, difficulties may be encountered which render them more or less valueless. Among these may be noted peripheral aberration, where contrary motion of the central reflex to that of the periphery is seen, often of such an amount that the important central movement can be observed only with difficulty, and akin to this is the well-known scissors movement. Other complicating factors arise from lenticular and corneal opacities. In addition to these, where a cycloplegic has been used, errors creep in from oblique pencils passing through the dilated pupil, varying completeness of the cyploplegic, and the wandering fixation of many patients.

At times, age, glaucoma, or other complications preclude the use of cycloplegics. Under these circumstances, dry, or the "dynamic" retinoscopy of Cross, must be resorted to. Many refractionists prefer to precede all other methods by a quick dry retinoscopy and become very proficient in the method, which does obviate some of the disadvantages of the cycloplegic method, but, on the whole, is less satisfactory to most examiners. It should be conducted in a darkened room on a range of at least 20 feet, if possible. In some instances a noncycloplegic dilator, such as 2.5-percent solution of neosynephrine, may be used.

Before closing this subject, one suggestion may be made which might be of value to the older refractionist. Despite the fact that in retinoscopy a virtual image is being observed at infinity, a better view of this image may be obtained by the addition of approximately a plus 1.0D. sph. to the distance correction of the observer. Such an addition will have no effect upon the result obtained. The addition may be incorporated in the retinoscope, or may be worn as a separate pair of spectacles.

It must be remembered, however, that all variations of this method are strictly objective and, therefore, leave much to be desired. For this reason, if for no other, it is usually impossible to do a retinoscopy, either dry, dynamic, or cycloplegic, then, making due allowance for the many complicating factors, hand the patient the prescription, telling him, "This is your proper correction; wear this and let me hear nothing further from you." It is very likely that he will comply with your instructions. All such measurements should be checked by other means.

Aside from the actual testing of the visual acuity by the use of charts of graded objects, letters, rings, or pictures of toys, I have found the astigmatic dial the most important single piece of apparatus available. With all due regard for the value of the cross cylinder as a check method, I believe that its use with letter charts alone, with or without previous retinoscopy, is responsible for more poor results in the correction of astigmatism than any other factor.

The astigmatic dial, after fogging, is a most accurate method of determining the axis of refraction of the eye as employed in the actual use of that organ, and, therefore, that axis at which the cylinder prescribed should lie. In many instances, however, the patient will not appreciate the differences of intensity of the lines without considerable instruction. Many a time I have heard a patient say, "My! This is the part

of the examination I dislike most. It makes me feel like a perfect fool." Of course, that is so. But in most cases, a little encouragement and explanation, with the avoidance of impatience and irritation on the part of the examiner, will produce the desired results.

The average patient with a low grade of astigmatism, when confronted with the dial, will declare the lines to be of equal intensity. But this decision cannot be accepted as final. The patient should be fogged at least 15 minutes, with the vision reduced to somewhat less than the best obtained by spheres. After this, it will be found that even small differences can be appreciated and the location accurately determined. In some cases, however, an artificial astigmatism must be produced and even exaggerated until the patient can recognize the difference in the intensity of the lines in the various axes so produced. Once having established this "know how," it is surprising how accurately the amount and axis of the astigmatism can be determined. In many cases, no other method is equal to this, when properly performed. Occasionally, it is best done under cycloplegia.

In this connection, a brief discussion of the keratometer and its place would seem to be in order. With the growth in reliance upon retinoscopy, which has increased since its simplification by the introduction of the magnificent self-illuminated retinoscopes, the streak instrument of Copeland, and others, the keratometer has been relegated to oblivion, especially in the offices of ophthalmologists of the younger generation, many of whom do not even know how to use it. This neglect is due to the fact that these instruments measure only the curvature of the anterior surface of the cornea. But, in my opinion, this total neglect is a great mistake. No method can compete with it in determining the axis and amount of astigmatism in the aphakic eye. As an example of this, I recently returned from a vacation to hear that a very critical case, in which a successful intracapsular cataract extraction had been done, had lost vision in the eye to such an extent that detachment of the retina, or minute macular hemorrhage, was suspected. The keratometer immediately revealed that the astigmatism, which had been 2.5D. in the horizontal meridian, had been reduced to 0.5D. and, with this change in the astigmatic correction and the proper spheres, the vision promptly rose from 20/75 to 20/12.

This is only one instance. I have frequently seen the results of excellent cataract surgery almost completely nullified by abominable refraction, frequently due to incorrect localization of the axis of astigmatism.

The same results can frequently be obtained by retinoscopy. But lenticular remains, or residual portions of capsule, and so forth, often render determination by this method extremely difficult, none of which interfere with keratometry. I have found it valuable, also, as a quick check of high grades of astigmatism, a large part of which is usually corneal.

A great advance was made in refractive technique with the introduction of the cross cylinder. The rapid change of cylinder axis produced by the flip of this instrument is far better appreciated than the slow change of the ordinary cylinders of the trial case, or even the more rapid changes of the refractor. In my opinion, it is best to reserve the use of the cross cylinder until at least an approximation of the amount and axis of astigmatism have been determined.

Flipping the cylinder back and forth along the correct axis will frequently make little difference in the sharpness of the chart being observed by the patient. The two positions do, however, result in somewhat different distortion of the letters, which may be confusing; but by shifting the axis of the cross cylinder, first to one side, then to the other, it is usually possible to obtain an immediate response as to which is better or worse, and thus the correct axis be rapidly spotted.

At times, however, especially if the lens before the patient's eye is an undercorrec-

tion, the patient will continue to shift the axis in one direction. Should such a situation arise, it is well to rest the eye by turning one's attention to the fellow eye, or by fogging both eyes for a time before returning to the attack.

Personally, probably due to my technique, if there is any great discrepancy between the two results, I prefer to test the point by actual use of the lenses in the waiting room, and to lean rather to the results obtained by retinoscopy and the astigmatic dial, or a compromise between all four methods, than to accept that of the cross cylinder as final. An accurate mastery of all is frequently necessary in complicated cases.

Unusual conditions

Now that these fundamental methods of refraction have been reviewed, I should like to consider briefly some of the rather more unusual conditions which are met with from time to time.

The presbyopic correction introduces many complications. The addition should be equal in at least 95 percent of all cases. If an unequal addition is required, the basic correction for distance should be looked upon with suspicion and rechecked. If the discrepancy persists, a neurologic examination is usually indicated. A previous diphtheria may be suspected, though the loss of accommodation resulting from this disease usually affects both eyes equally and probably will have been recognized previously.

The most frequent error in correcting presbyopia, either in the phakic or aphakic eye, is toward overcorrection. For some reason or other, the patient will almost certainly select too strong a correction. Seldom is it the other way around. If the corrected distant vision is good, more than +2.25D. is seldom required by the phakic eye, and +2.5D. is almost always satisfactory for the aphakic eye, following a good cataract operative result. Many ophthalmologists seem to prefer +3.0D., which I have found most unsatisfactory for the average patient. In making the proper choice, a consideration of the patient's occupational needs cannot be overemphasized.

Vertical imbalance in anisometropia presents complications which are frequently overlooked by the refractionist, but which may be the cause of considerable discomfort for the patient. Prentice's law states that, "the amount of prism at any point in a lens is equal to the power of the lens in diopters multiplied by the decentration in centimeters," or, in other words, decentering a one diopter sphere one centimeter will produce one diopter of prism. In the act of reading the eyes are dropped, as a rule, 10 mm. below the optical center of the lens. If the power of the lenses is equal, this is of no consequence, but if not, a prismatic effect is produced. This is easily computed in the case of spherical lenses, but complications arise when cylinders are included in the prescriptions. For instance,

O.D. +1.0D. sph.
O.S. +3.5D. sph.

At 10 mm. below the center of the lens, the computation is,

3.5D. − 1.0D. = 2.5 prism diopters difference between O.D. and O.S.

With cylinders included, we find more complications: for example,

A

Rx: O.D., +2.5D. sph. ⊖ −2.25D. cyl. ax. 30°
O.S., +2.5D. sph. ⊖ −3.25D. cyl. ax. 180°

B

Rx: O.D., −0.75D. sph. ⊖ +1.5D. cyl. ax. 85°
O.S., −2.5D. sph. ⊖ +3.0D. cyl. ax. 140°

At the reading depth of 10 mm., in Rx A there is an unequal prismatic effect of 1.37, whereas in Rx B the inequality is found to be 0.26, an insignificant amount.

These results are obtained by considering not only the vertical power of the sphere, but also that of the cylinder. This latter amount varies not only with the strength of the cylinder, but also with the relation of the axis of the cylinder to the vertical meridian.

The accompanying Table 1 is used for

TABLE 1

FOR COMPUTATION OF PRISMATIC POWER OF THE CYLINDER IN VARIOUS MERIDIANS AT 10 MM. BELOW THE OPTICAL CENTER OF THE DISTANCE LENS WHEN THE POWER OF THE CYLINDER IS ONE DIOPTER

(From the Univis Lens Company Bulletin.)

Axis for Right Eye		Axis for Left Eye	Axis for Right Eye		Axis for Left Eye
0	1.000△	180			
5	1.010△	175	95	**0.010*△*	85
10	1.004△	170	100	**0.004*△*	80
15	0.983△	165	105	0.017△	75
20	0.947△	160	110	0.053△	70
25	0.898△	155	115	0.102△	65
30	0.837△	150	120	0.163△	60
35	0.765△	145	125	0.235△	55
40	0.685△	140	130	0.315△	50
45	0.600△	135	135	0.400△	45
50	0.512△	130	140	0.488△	40
55	0.423△	125	145	0.577△	35
60	0.337△	120	150	0.663△	30
65	0.255△	115	155	0.745△	25
70	0.181△	110	160	0.819△	20
75	0.117△	105	165	0.883△	15
80	0.064△	100	170	0.936△	10
85	0.025△	95	175	0.975△	5
90	0.000△	90	180	1.000△	0

* Figures in italics denote △ base DOWN for plus and △ base UP for minus.

this computation of the prismatic power of the cylinder in the various meridians at 10 mm. below the optical center of the distance lens when the power of the cylinder is one diopter. If the cylinder power is more or less than one diopter, all that is necessary is to multiply the figure found for one diopter by the strength of the cylinder prescribed.

For correct computation in bifocal lenses, it is necessary to know where the optical center of the distance portion lies. Modern lenses are usually ground so that the optical center coincides with the geometric center, but due to the odd shape of many lenses, it is more accurate to prescribe the size of the segment, not as height from the bottom of the lens, but as distance from the optical center.

I wish to acknowledge the courtesy of the Univis Lens Company in permitting the use of the two tables shown in this paper, and also Figures 1, 2, and 3, all taken from their bulletin, "The Correction of Vertical Imbalance."

In a bifocal, the reading depth is modified by the size of the segment relative to the size of the entire lens. For example, take

Rx: O.D., +1.0D. sph.
O.S., +4.0D. sph. ⊃ −0.5D. cyl. ax. 180° = 3.50
Add +1.25D. sph. Segments 17 mm. high
Lens size 44 horizontal × 40 vertical

Optical center	20 mm. high
Segment top	17 mm. high
	3 mm. from segment top to optical center

The reading point of a Univis D, for instance, is five mm. from the top of the segment; the reading depth in the prescription above is, therefore, three plus five, or eight mm. The result is multiplied, not by 10 mm., but by 0.8 mm.; that is, at the reading level, the amount of prismatic imbalance is not 2.50 P.D., but $2.50 \times 0.8 = 2.00$ P.D.

In the following example, with cylinders at oblique axes complicating the problem, their power in the vertical meridian must be computed according to Table 1, thus:

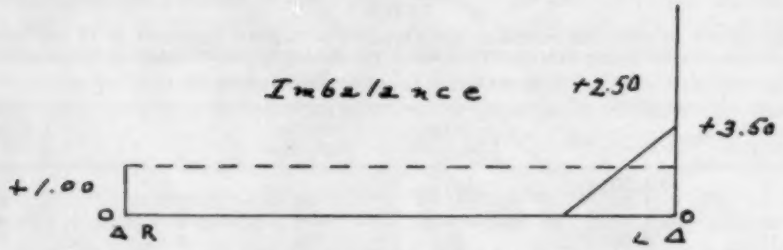


Fig. 1 (Post). For use in complications of vertical imbalance in anisometropia.

Rx: O.D., +3.0D. sph. ⊃ −2.5D. cyl. ax. 110°
O.S., +0.75D. sph. ⊃ −0.25D. cyl. ax. 60°
Add, +1.00 Segments 15 mm. high
Lens size 40 horizontal × 36 vertical

Mechanical optical center	18 mm.
Segment height	15 mm.
	3 mm.
Reading level	5 mm.
Reading depth	8 mm.

From the table,
O.D., +1.0D. cyl. ax. 110° = 0.053
O.S., +2.5D. cyl. ax. 110° = 0.053 × 2.50 = 0.132
or,

+3.00
−0.13
+2.87

O.S., +1.0D. cyl. ax. 60° = 0.163
+0.25D. cyl. ax. 60° = 0.163 × 0.25 = 0.04050
or,

+0.75
−0.04
+0.71

The imbalance at reading distance 10 mm. below horizontal would be 2.16; at 0.8 it would be 0.8 × 2.16 = 1.73. (See Figure 2.)

For the correction of vertical imbalance, a prism may be ground into one or the other lens. It should be noted that the base of the prism must be upward and that the lens for the right or left eye must be selected wherever such grinding will correct the imbalance. In presbyopes, up to 1.5 P.D. of such imbalance may be corrected by selecting segments ground so that their optical centers are displaced up or down from the center of the segment.

Table 2 shows the effect obtained by displacement of the segment centers from one mm. to six mm. in additions of from +0.75D. sph. to +3.50D. sph. For example: If the Rx calling for a +2.25D. add showed an imbalance of 1.20 P.D., the closest compensation shown on the chart is 1.13. This is obtained by varying the optical centers five mm.; therefore, shapes 4 with 9, or 5 with 10, would be equally satisfactory. In other words, all that is necessary is to multiply the strength of the segment by the number of mm. between the centers of the right and left segments.

For instance, in the example given above, should the addition be +1.75D., using segment 4 and 10, a displacement of 6.0 P.D. would be obtained, and 6 × 1.75 = 1.05 P.D.

If a greater decentration than five prism diopters is required, suppression of one or the other eye will result. It is not uncommon to have patients remark that they frequently find themselves closing one eye during read-

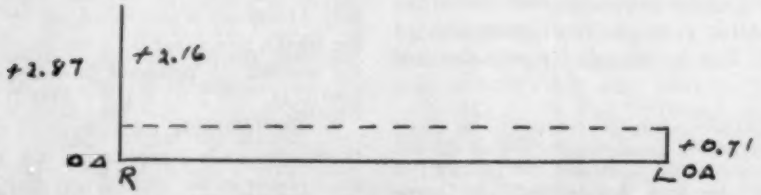


Fig. 2 (Post). Imbalance at reading distance 10 mm. below horizontal.

TABLE 2

EFFECT OBTAINED BY DISPLACEMENT OF THE SEGMENT CENTERS

(From the Univis Lens Company Bulletin.)

Add	1 mm.	2 mm.	3 mm.	4 mm.	5 mm.	6 mm.
+0.75	0.08△	0.15△	0.23△	0.30△	0.38△	0.45△
+1.00	0.10	0.20	0.30	0.40	0.50	0.60
+1.25	0.13	0.25	0.38	0.50	0.63	0.75
+1.50	0.15	0.30	0.45	0.60	0.75	0.90
+1.75	0.18	0.35	0.53	0.70	0.88	1.05
+2.00	0.20	0.40	0.60	0.80	1.00	1.20
+2.25	0.23	0.45	0.68	0.90	1.13	1.35
+2.50	0.25	0.50	0.75	1.00	1.25	1.50
+2.75	0.28	0.55	0.83	1.10	1.38	1.65
+3.00	0.30	0.60	0.90	1.20	1.50	1.80
+3.25	0.33	0.65	0.98	1.30	1.63	1.95
+3.50	0.35	0.70	1.05	1.40	1.75	2.10

ing or sewing, though in the latter binocular vision is more reluctantly given up, as depth perception is more important in sewing than in reading. In some such cases, considerable training may be necessary to restore binocular fixation after the proper prismatic correction has been given. Occasionally, the patient may have learned to compensate for a part of this imbalance. If so, it may be best to correct, at first, for only the uncompensated portion. Most grinding laboratories are equipped with facilities and tables for computing the amount of prismatic correction required, but the ophthalmologist should also be in a position to make these measurements.

Without entering into the above calculations, a rough estimate may be obtained of the prism necessary to create balance of the two visual lines in the nonpresbyopic patient by holding the Maddox rods over the glasses which are to be prescribed, as they are worn in the trial frame. In the presbyope, such a method is not possible, but a fair idea as to the amount of correction necessary may be obtained by use of the Maddox rods over the reading segment of the former glasses.

In the fitting of glasses for high refractive errors, precautions must be taken concerning the size difference of the images. In addition to making sure that each eye is properly corrected, its relation to the fellow eye must be given the most careful study. An extreme situation is that of the patient who has had one eye operated upon for cataract, with a good visual result, and an unoperated eye having good vision, also. In such a case, binocular single vision is impossible, excepting through the intervention of contact lenses, a consideration of which will be taken up presently.

In conditions short of this extreme, much can be done. In fitting glasses, especially of high power, there are three primary considerations concerning the proper position of the lenses before the eyes. In the first place, the pole of the lens should coincide with the visual line, as has been previously noted, malposition in this respect resulting in a prismatic effect. In addition, the result of tilting the lens about any axis must be taken into consideration. For instance, in cases where it is desirable to place the lenses before the eyes in an unusually pantoscopic position, that is, tilting them forward along the horizontal axis, the power of the cylinder will be increased in that meridian. To take an example, in the case of a 4.00 diopter lens tilted 20 degrees, the cylinder produced will amount to as much as 0.50 diopter. A lens

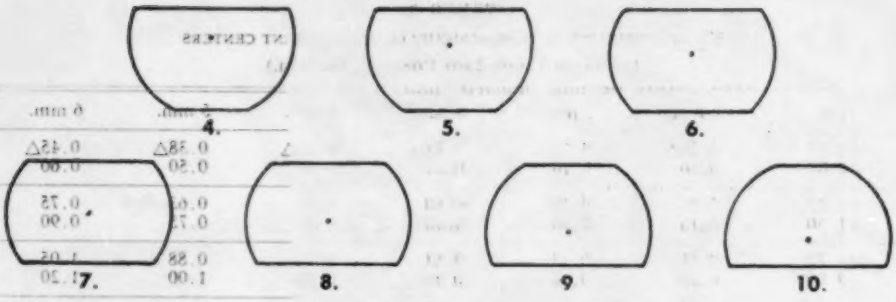


Fig. 3 (Post). Displacement of segment centers.

having the power +4.0D. sph. ⌒ +1.0D. cyl. ax. 90°, tilted along the 180-degree meridian, will have the power of the cylinder decreased. If, on the other hand, the lens were tilted along the vertical meridian, the power of the cylinder would be increased. It is on this account that patients at times find that vision is improved by looking obliquely through the lenses placed before the eyes. A similar change may occur in passing from the distant vision straight ahead to the downward position of close work. This change will occasionally cause trouble, and should be looked for in cases where otherwise unexplained difficulties arise. This may be done by asking the patient to observe a reduced astigmatic dial held in the reading position, then making corrections, accordingly.

In the second place, the posterior focus of the lens must coincide with the far-point of the eye. It is stated that an ametropic eye, properly corrected for distance, is the same as an emmetropic eye without a lens. This is not exactly so, though it is usually assumed to be true.

From Figures 4 and 5, it will be seen that, since the principal focus F of the lens and the far-point of the eye lie behind the convex lens, the lens will always be weaker than the hypermetropia which it corrects, and that the weaker it is, the farther it should be placed from the eye. (This does not apply when the distance for which the eye is adapted is less than the focal distance of the lens, as in extremely high degrees of hypermetropia, or particularly in aphakia.)

It can also be seen that the contrary is true in myopia. The farther away such a lens is placed from the eye, the stronger it must be.

The third requirement is that the second principal point, or plane, of the lens should coincide with the anterior principal focus of the eye. This must be observed if no change in size of the retinal image is desired. Figures 6, 7, and 8 show why this is so.

In the case of a minus lens, the size is decreased by removing the lens farther from

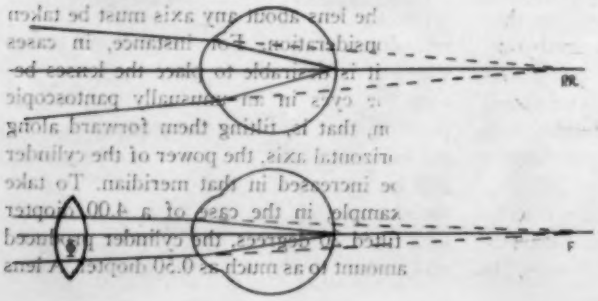


Fig. 4 (Post). Hyperopia. (PR) Punctum remotum of eye: far point. (F) Posterior principal focus of lens. (Φ) Anterior principal focus of eye.

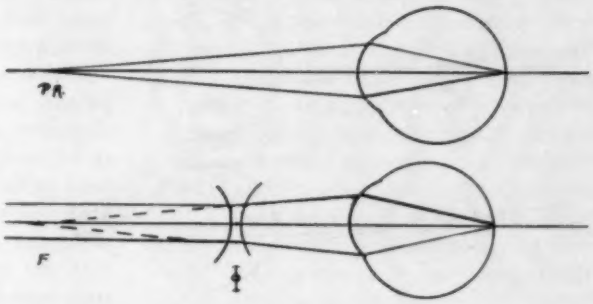
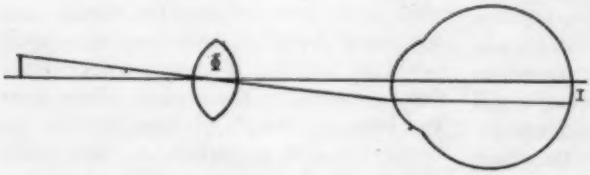
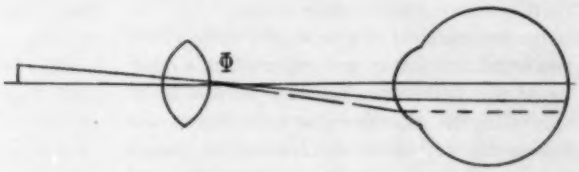


Fig. 5 (Post). Myopia. (PR) Punctum remotum of eye: far point. (F) Posterior principal focus of lens. (Φ) Anterior principal focus of eye.

Fig. 6 (Post). The plane of the lens should coincide with the anterior principal focus of the eye.





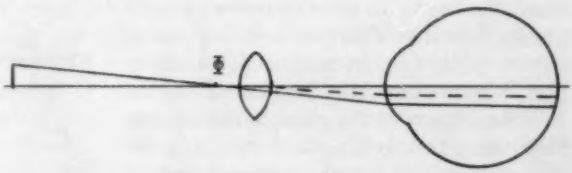


Fig. 7 (Post). The plane of the lens should coincide with the anterior principal focus of the eye.

the eye than the anterior principal focus, and increased when placed closer. The contrary is true with convex lenses.

From these latter facts, it follows that the posterior principal plane of the hypermetropic lens should be as far in front of the eye as possible, and that of the myopic lens as close to the eye as possible. A look at Figure 9 of two meniscus lenses, plus and minus, will show how nicely they fit into this picture.

Without going into the optical principles, it can be seen that the optical center of the plus meniscus lies anterior to the lens and

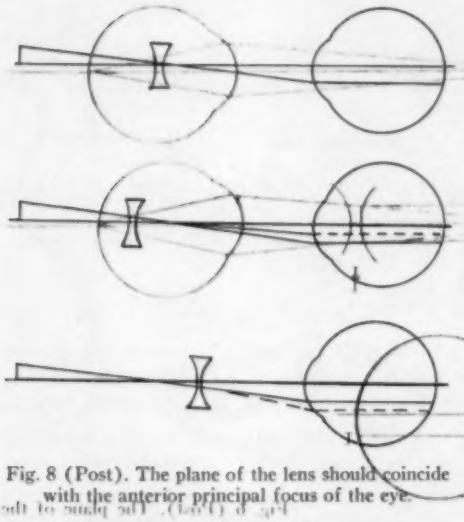


Fig. 8 (Post). The plane of the lens should coincide with the anterior principal focus of the eye.

that of the minus lens behind the lens, or between it and the eye. If this fact is taken into consideration in the fitting of glasses, much can be done by the proper placement of the lenses to correct anisometropia and thereby increase the comfort of such patients. Time and space, and also the stated intent of this discussion, will not permit further elaboration of these points.

In the case of the aphakic eye, where powerful plus lenses are required, this quality of the meniscus lens can be seen to be of special value. Whether the case is one for monocular or binocular adjustments, it can be seen from the criteria previously laid down that some form of meniscus lens is usually desirable. There is, however, an exception to this rule. In cases of high astigmatism it is impracticable, because of the required thickness of the glass, to use a minus base curve. It is best to be content to grind the minus cylinder on the posterior surface, and the plus sphere on the anterior surface of the lens. Later on, approximately six months after the cataract extraction, Panoptik, or similar lenses, may be prescribed to eliminate many of these difficulties. The cost of these lenses makes earlier use of them prohibitive in most cases, because of the frequent need for making one or two changes in the correction during this period.

I have never succeeded in becoming 100-percent accurate, despite the use of the distometer in all cases, in prescribing cataract lenses so that the finished glass did not have to have plus or minus spherical additions in order to obtain the best possible vision, and I have a definite understanding with the optician grinding the lenses that such resurfacing will probably be expected of him. The patient is also warned of this probability and, in the case of out-of-town patients, they are asked to return for delivery of their glasses at the time specified by the optician, prepared to spend the night in town, while likely adjustments are being made.

One word of caution concerning the adjustment of lenses to the binocular aphakic; while it is desirable that the vertical and horizontal deviations be corrected as accurately as possible, it is well to remember that, especially in those cases where there has been any length of time elapsing between the two operations, a considerable amount of adjustment will take place after

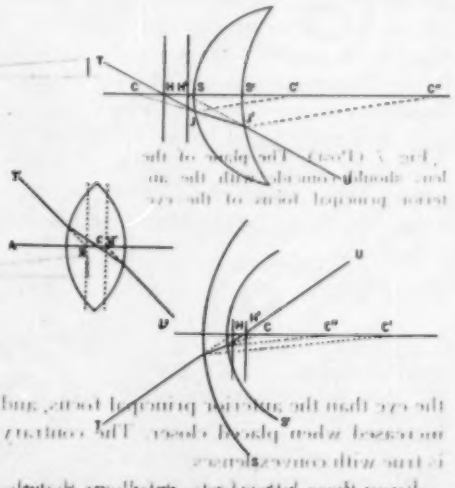


Fig. 9 (Post). The principal plane of the hypermetropic lens should be as far in front of the eye as possible, and that of the myopic lens as close to the eye as possible.

a comparatively short interval. An opportunity for such adjustment should be allowed before including prisms in the prescription.

Do not hesitate to make changes in the lenses from time to time because of financial considerations. If the patient can afford the operation at all, he can afford to be made comfortable and to have the finest vision possible. With anything less, the operator's reputation will suffer accordingly.

In cases having good vision in both eyes, one phakic, the other aphakic, the only practical way to secure binocular third dimensional fusion is by the use of contact lenses. A number of well-known ophthalmologists are enthusiastic concerning the results obtained. In my own experience, I have found it very difficult to persuade patients to adopt them, especially when they learn that for close work additional glasses must be worn over the contact lenses.

Without such lenses, diplopia practically always results. This is due, firstly, to the high degree of anisometropia which results in an insuperable muscular imbalance whenever the eyes are rotated away from the optical centers of the two lenses, and, secondly, to the marked size difference in the retinal images in the two eyes. The image of the aphakic eye, corrected by the use of a spectacle lens, will be 33⅓ percent larger than that of its uncorrected emetropic fellow, when the lenses are placed about 13.76 mm. from the cornea.

Both these difficulties are greatly reduced by contact lenses, which may be worn over both eyes, or, in many cases, over the aphakic eye only. With the contact glass, the line of vision always passes through the optical center, eliminating most of the muscular imbalance, and its nearness to the cornea relatively reduces the size of the actual image on the retina. A convex lens, it will be recalled, worn within the anterior focus of the eye, which in the normal is 15.80 mm., but in aphakia is 24.40 mm. in front of the cornea, will reduce the size of the image. The contact lens is placed almost at the principal points of the uncorrected aphakic eye, thus gaining the maximum minimizing effect. By the use of such lenses, the size difference is reduced from 33⅓ percent to approximately 10 percent, which, in practical experience, is claimed to cause little difficulty.

Many more niceties of refraction could be cited, if space were to permit, almost ad infinitum, so complex is the problem. A few words, however, must be said concerning the problem of ocular neuroses.

No one can doubt the very great influence of the mental attitude of the patient upon his ocular condition. No one has failed to observe the patient who comes to the clinic or office, with his glasses practically hanging on one ear, tilted at about 10 degrees from the horizontal, remarking: "Oh, my glasses are all right and give me no trouble, but I just thought they should be looked over," but who, later on, when after laborious study a careful refraction has been done and glasses prescribed, will return, complaining bitterly over a mere three-degree shift of one axis. Some, I am sure, only desire that a little more fuss be made over them; others have become eye-conscious and are looking for trouble.

No phase of refractive disturbances presents more challenging problems than those of ocular neuroses. Where such conditions are suspected, every effort of the physician should be directed toward the recognition of the difference between symptoms resulting from actual errors of refraction and those complaints of emotional origin that closely resemble them. Patients come to the oculist for a wide variety of disorders which they believe and hope arise from need of glasses, or a change of lenses. They are often wrong. So, unfortunately, are the physicians who see them.

There are many symptoms common to both actual and emotional disorders, such as asthenopia, headache, impaired vision, irritation and inflammation of the eye, inability to perform close work, nausea, vomiting, and

others. Blepharospasm and blinking may result from such causes, or from emotional upsets. In many cases, the actual organic trouble may give rise to the functional disorder in what is known as functional overlay. For instance, exaggeration of normal phenomena may thus be a factor, such as physiologic diplopia, and so forth.

Neurotic complaints are more easily detected if their mode of production is understood. In all cases there is something that marks them as spurious, that is, the symptoms do not conform to known physiologic phenomena, but are figments of the subconscious mind, which does not know exactly how such symptoms should be manifested.

Such disturbances arise from numerous causes, fear, temptation, or desires incompatible with conscience. The conscious mind thrusts them down into the subconsciousness, then the subconsciousness devises a form for their return that may be acceptable, a trick known as conversion neurosis.

Functional manifestations, as indicated, are not developed in an orderly and consecutive fashion, but rather illogically. They must be drawn from the experience of the individual. For instance, a lady, whose eyes I knew from previous observation and present examination to be entirely normal, called me in grave distress over what she thought to be rapid and total failure of vision. She complained of "darkness, always darkness" shutting her in. The vision, fields, refraction, tension, and so forth, were entirely normal, but she nearly drove her family and doctors frantic with her constant and tearful appeals for help. No help was forthcoming until a long discussion disclosed fears of a number of months' standing that a dear friend, who had undergone cataract surgery, and later suffered detachment of the retina, was going blind. When these facts were brought to light, and the transferral of these fears for her friend to herself was recognized, her joy and relief were unbounded and showed in every aspect of her being.

Psychic blindness is occasionally met with. It was frequent during prohibition, when alcoholics were prone to drink what came their way and were often fearful of the well-known blindness following the ingestion of wood alcohol. I well recall attending such a patient one night in his home in the backwoods, with the entire clan about him, looking daggers at me, should I fail to save him. I am still alive.

Many such cases occur, but are all too frequently overlooked, or made light of, because of misunderstanding and inability, or unwillingness, of the examiner to give the necessary time and effort to probe to the bottom of the disorder.

The conscious mind is orderly and systematic, whereas the subconscious mind is illogical, the region of dreams, with changes of scene backward and forward, without limitations of time or space. The symptoms resulting from the subconscious mind should, therefore, be recognizable as such. The disorders so produced, though known to be spurious, cannot be overlooked, since the pain and discomfort produced by them are real and often severe, and require that something be done about them.

Neuroses differ from malingering in that those suffering from the former are co-operative and desire to be cured, while those in the second group have carefully built up their symptoms complex, and the last thing they desire is to have it broken down. Probably pure malingering is rare. It is almost always the product of a twisted personality. The fields developed by the hysteric and malingerer have little in common. The one shows the classical, tubularlike forms, the other markedly irregular and irrational ones.

Many mentally disturbed eye patients occupy a midposition between psychoneurotics and psychosomatics. Authorities describe differences between the two types. In the former, the outward tension phenomena are present, but are absent in the latter. It is believed that the psychosomatic patient does not have the ability to recognize this suppressed anxiety as a physical symptom, while the other does.

Ciliary spasm may be a psychosomatic

symptom and its true nature may only be disclosed by the use of cycloplegia. "Blind staggers" or "black-outs," known scientifically as amaurosis fugax, are another form of such phenomena. Migraine, also, may fall into this category, but is now thought by many to be of vasomotor origin.

Such disturbances affect the refractionist in that they should be understood, in order that useless and misdirected efforts to effect a cure in such conditions by minute changes in the correction of refractive errors may be avoided.

The subject of neurosis of ocular origin is almost endless, so that only a few of the major indications can be noted here, and are called to your attention in order that they may not be overlooked.

In closing, I should like to emphasize as strongly as possible the importance of obtaining the vision of all patients on their first examination, and making an attempt by refraction to obtain the best vision possible before proceeding to other examinations, such as dilating the pupils, or taking the tension, after which refraction cannot be done. By so doing, many an embarrassing moment may be avoided, such as might arise should the patient ask at the end of the visit whether it is possible to improve the vision by a change of glasses, when you do not know, and cannot tell without requesting the patient to return, often from out of town, for a subsequent visit. It is always well, furthermore, to bear in mind that many an apparently obscure diagnosis can be cleared up by a careful check of the refraction, thereby avoiding long and futile misdirected efforts.

Such, then, are a very few of the complexities confronting the refractionist. Observation and understanding, and the ability to overcome these complexities, are the marks of the good refractionist. The more of the refinements mastered and applied to the correction of refractive errors, the more satisfactory will be the results that are obtained. Great patience, much time, and great understanding, are essential to the achievement of the best results. There is no royal road to success.

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RETINAL DYSPLASIA*

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Several years ago the term leukokoria was introduced as a nonspecific descriptive name for the white pupillary reflex produced by opaque tissue in the retrolenticular space. This designation was suggested with the full realization that it grouped together a number of distinct and unrelated disorders united only by a conspicuous clinical similarity. In the ensuing years, the concerted clinical and investigative effort associated with the study of retrolental fibroplasia has done much to differentiate the various disorders in the leukokoria group. As a result, it is now recognized that leukokoria may be the clinical expression of congenital anomalies, retrolental fibroplasia, acquired inflammation, or neoplastic disease.

A form of congenital aberration in the leukokoria group is retinal dysplasia.† Early references to this condition appeared in 1875[1] and 1897,[2] and more recently Krause

* From the Institute of Ophthalmology of The Presbyterian Hospital. We wish to thank the Armed Forces Institute of Pathology for the use of their material and their help with this paper.

† In a comprehensive sense, the term retinal dysplasia may be applied to any abnormal differentiation of the retina after formation of the anlage. However, in this report we are restricting this term to the group of cases showing dysplastic differentiation of the sensory retina in conjunction with nonocular abnormalities.

(1946)[3] described cases with retinal anomalies and general developmental disorders. The true nature of retrolental fibroplasia was not appreciated at the time of this report so that Krause included cases of both retrolental fibroplasia and retinal dysplasia in the material presented. In 1950, one of us (A. B. R.), in collaboration with Blodi[4] distinguished retrolental fibroplasia from the congenital anomalies of retinal dysplasia and presented a summary of the pertinent literature and eight documented cases with multiple congenital anomalies. Meyer-Schwickerath described a single patient with this syndrome in 1953, and MacDonald and Dawson[6] added a typical case report in 1954. Other cases[7,8] are probably reports of retinal dysplasia but the lack of histologic documentation prevents complete acceptance.

Since 1950, additional experience with retinal dysplasia has permitted a more comprehensive understanding of this syndrome. The purpose of this report is to define retinal dysplasia clinically and anatomically on the basis of this cumulative experience, and to relate this entity to other forms of ocular maldevelopment.

Retinal dysplasia is a developmental aberration present at birth and characterized by bilateral ocular anomalies, diffuse systemic malformations, and a familial tendency. Most infants with this syndrome are born at term, and there is no relationship between this entity and prematurity.

Clinically, the eyes of these affected patients are generally somewhat smaller than normal though the degree of microphthalmos may vary from mild to extreme. The anterior chamber is usually shallow, remnants of the pupillary membrane may be present, and the iris may be restricted by extensive posterior synechias. Cataractous changes may occur, but the lens is generally clear enough initially to permit visualization of a white mass of vascularized tissue in the retrolenticular space. Occasionally, large ciliary processes may be visible as they insert into the periphery of this central mass and combine with

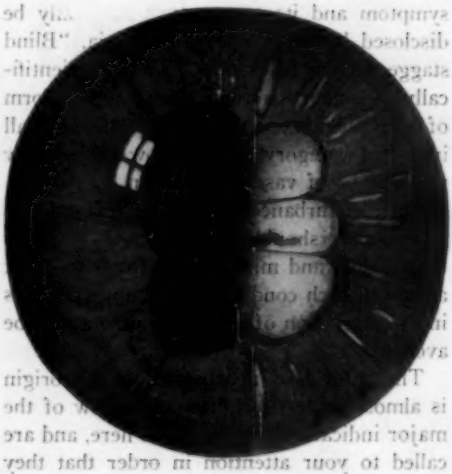

Fig. 1 (Reese and Straatsma). Clinical appearance, showing remnants of the pupillary membrane, pupil irregularity, and a white mass of vascularized tissue in the retrolental space. (T. H. Uhl No. 26428.)

it to prevent any further survey of the globe interior. In some cases, however, the retrolental membrane occludes only a portion of the pupil so that persistent elements of the primary vitreous or a retinal fold may be visualized. These retinal folds are attached to the persistent hyaloid vessels and extend from the disc to the fibrovascular plaque on the back of the lens. These abnormalities are sufficient to account for complete blindness or a severe reduction in visual acuity.

With the passage of time these eyes are subject to an elevation of intraocular pressure that is related to malformation of the filtration angle or the result of intraocular heinorrhage. This elevation in pressure may produce the steamy cornea and congestion of acute glaucoma or the progressive enlargement of buphthalmos.

Associated with these ocular abnormalities are a variety of congenital malformations affecting the central nervous system and other body systems. Mental retardation and hydrocephalus of the internal obstructing type are the principal central nervous system anomalies. Numerous cardiovascular defects,

polydactylism, cleft lip and palate, omphalocele, and malrotation of the intestines are other diverse defects sometimes encountered. These extensive anomalies affecting critical segments of the body may cause the death of these patients in the neonatal period. In other cases the patients survive for a longer time, but this seems to reflect a milder form of the basic process.

Appraisal of the familial or hereditary factor is of importance in advising the parents of affected offspring and as a clue to etiology. This feature is discussed later in the paper but it should be stated now that some familial tendency seems apparent.

Material

Following this introductory clinical sketch, consideration may be given to specific cases which were assembled from the pathology collection of the Institute of Ophthalmology, and the Armed Forces Institute of Pathology.* This histologic material was supplemented by a group of clinical cases observed in the Children's Eye Clinic of the Institute of Ophthalmology, and in other departments of Columbia-Presbyterian Medical Center.

Seventeen previously unreported cases of retinal dysplasia were studied. These cases show variations in the disease pattern but all present bilateral congenital ocular disease with complete or partial retinal detachment in addition to one or more developmental anomalies affecting other systems. The globes of 10 infants in this series were examined histologically and the diagnosis of retinal dysplasia confirmed. In the other seven cases (three fatal and four surviving) the eyes have not been studied so that the diagnosis in these cases is clinical and presumptive.

Table 1 summarizes the salient features of these 17 cases. These infants were the product of a normal gestation period and an uncomplicated delivery remarkable only in showing hydramnion in Cases 2 and 6, and a threatened miscarriage early in the gestation of Case 12. All but one of these births occurred at full term and there was no sex preponderance evident in this group. Of particular significance is the mortality of 70 percent in this series. The neonatal period was particularly hazardous for these patients and most of the fatalities occurred during the first year of life.

Pathology

A. Ocular

The common feature of the ocular pathology in these cases is a developmental anomaly involving the inner layer of the optic cup. This layer deviates from its normal pattern of orderly growth and differentiation by evidencing a proliferative infolding of its external layers. In section, this infolding is seen as a series of straight or branching tubes composed of abortive elements of the rod and cone layer, the external limiting membrane, and the outer nuclear layer. When sectioned serially it is often possible to demonstrate a communication between the lumen of these tubes and the subretinal space. However, as the eye enlarges and the infolding progresses, the communication between the subretinal space and the tubes becomes obliterated so that the tubes appear as isolated round or oval rosettes. These branching

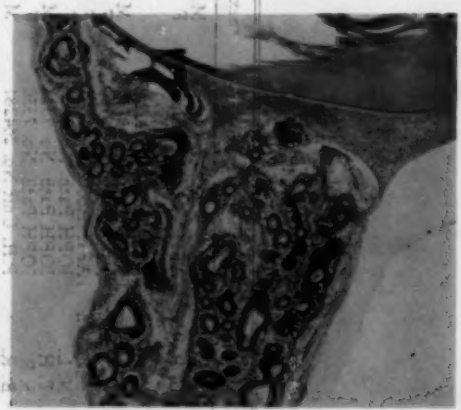

Fig. 2 (Reese and Straatsma). Dysplastic retina and persistent fibrovascular tissue in the retrolental space. (AFIP No. 45389, hematoxylin-eosin, ×50.)

* A single case was studied through the courtesy of The Jamaica Hospital, Jamaica, New York.

TABLE 1

SUMMARY OF 17 CASES REPORTED

Case	Name	Identification	Sex	Clinical History	Disease Course	Ocular Pathology	Autopsy
1	T.B.	AFIP Acc. No. 514013	M	Multiple anomalies	Dead (age 3 mo.)	Retinal dysplasia	
2	G. P.	AFIP Acc. No. 482859	F	Premature birth with multiple anomalies	Dead (age 45 min.)	Retinal dysplasia	Multiple anomalies
3	Unknown	AFIP Acc. No. 523225			Dead (age 2 da.)	Retinal dysplasia	Multiple anomalies
4	Unknown	AFIP Acc. No. 45389	M	Multiple anomalies	Dead (age 1 mo.)	Retinal dysplasia	Multiple anomalies
5	N.E.	AFIP Acc. No. 69016	F	Hydrocephalus	Dead (age 4 mo.)	Retinal dysplasia	
6	Unknown	AFIP Acc. No. 80346	F		Dead (age 1 da.)	Retinal dysplasia	Multiple anomalies
7	N. L.	IOPH Path. No. 4625R	F	Multiple anomalies	Dead (age 1 yr.)	Retinal dysplasia	
8	T. H.	IOPH Path. No. 7324	M	Multiple anomalies	Dead (age 10 da.)	Retinal dysplasia	
9	S. R.	IOPH Path. No. 7350	F	Multiple anomalies	Dead (age 1 mo.)	Retinal dysplasia	Multiple anomalies
10	B. R.	P.H. Unit No. 264281	M	Multiple anomalies Clinical retinal dysplasia	Dead (age 6 mo.)		Multiple anomalies
11	G. R.	Jamaica Hosp. No. 3151A	F	Multiple anomalies Opaque white masses in the lens area	Dead (age 4 da.)		Multiple anomalies
12	J.B.	P.H. Unit No. 859848	F	Hydrocephalus Clinical retinal dysplasia	Dead (age 15 mo.)		
13	D. R.	AFIP Acc. No. 331935	M	Anomalous frontal encephalocele	Living (age 3 wk.)	Retinal dysplasia	
14	J. H.	Children's Clinic No. 594	M	Mental retardation Clinical retinal dysplasia	Living (age 4½ yr.)		
15	F. M.	P. H. Unit No. 741954	M	Mental retardation Clinical retinal dysplasia	Living (age 9 yr.)		
16	L. H.	Children's Clinic No. 907	F	Mental retardation and convulsions Clinical retinal dysplasia	Living (age 13 mo.)		
17	M. H.	Children's Clinic No. 63	F	Mental retardation Clinical retinal dysplasia	Living (age 12 yr.)		

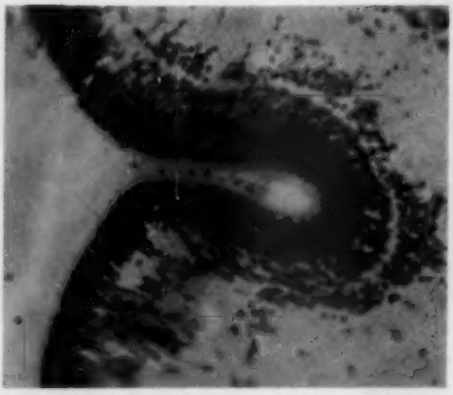

Fig. 3 (Reese and Straatsma). Retinal section showing infolding of dysplastic tissue. Communication with the subretinal space is apparent. (I.O.P.H. No. 7324, AFIP No. 846392, hematoxylin-eosin, ×305.)

Fig. 4 (Reese and Straatsma). Serial section in area corresponding to Figure 3 demonstrates a bridge of tissue between the developing rosette and the subretinal space. (I.O.P.H. No. 7324, AFIP No. 846392, hematoxylin-eosin, ×305.)

tubes of aberrant retinal growth and the associated round or oval rosettes are characteristic of retinal dysplasia. Typically, they consist of a clear central lumen, an abortive rod and cone layer, a fine limiting membrane, and a layer of dark nuclei. In some cases a plexiform layer and a second ring of nuclei surround the above structures.

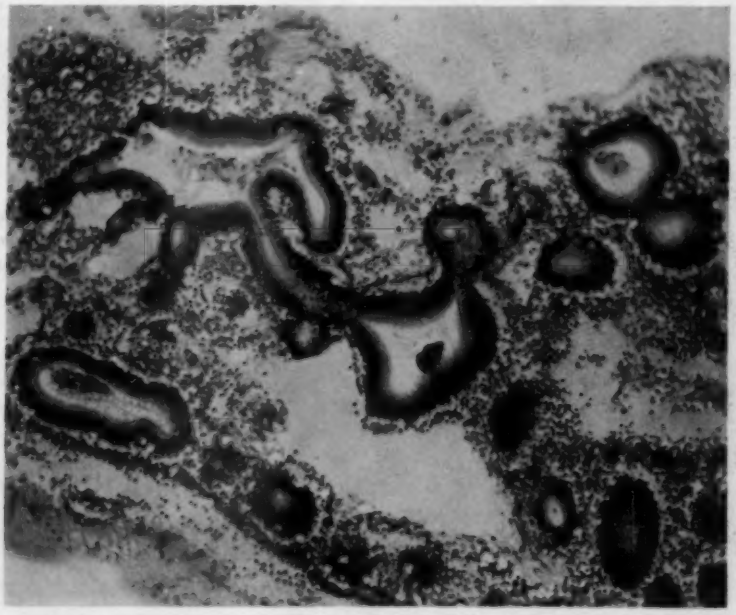

Fig. 5 (Reese and Straatsma). Retinal dysplasia. The round or oval rosettes and branching tubes of cells are characteristic. (AFIP No. 45389, hematoxylin-eosin, ×115.)

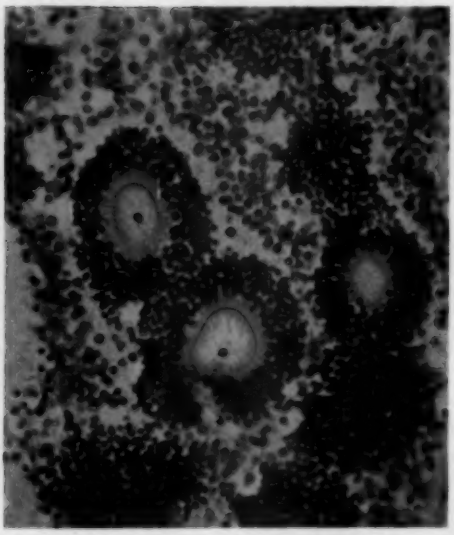

Fig. 6 (Reese and Straatsma). Dysplastic rosettes consist of a central lumen, an abortive rod and cone layer, a fine limiting membrane, and a layer of dark nuclei. (AFIP No. 45389, hematoxylin-eosin, ×305.)

The proliferative tubes and rosettes of retinal dysplasia are quite distinct from the neoplastic rosettes of retinoblastoma. In neoplastic retinal growth the cells aggregate in small almost spherical clusters, so that the rosettes are nearly round in whatever plane they are sectioned. Consequently, the eliptical rosettes and the straight or branching tubes of cells are unique in dysplasia and are never seen in retinoblastoma. As a further differentiation the rosettes of dysplasia are considerably larger, contain more cells, and may possess more cell layers than the rosettes encountered in retinoblastoma.

In addition to the formation of rosettes, the retinal dysgenesis is evident in the disorganization of the general cellular pattern. Immature cells of all apparent degrees are dispersed in the abnormal tissue and ganglion cells appear less numerous than usual. The process diffusely affects the retina so that ganglion cells are decreased even in the non-detached areas of the retina—a factor that

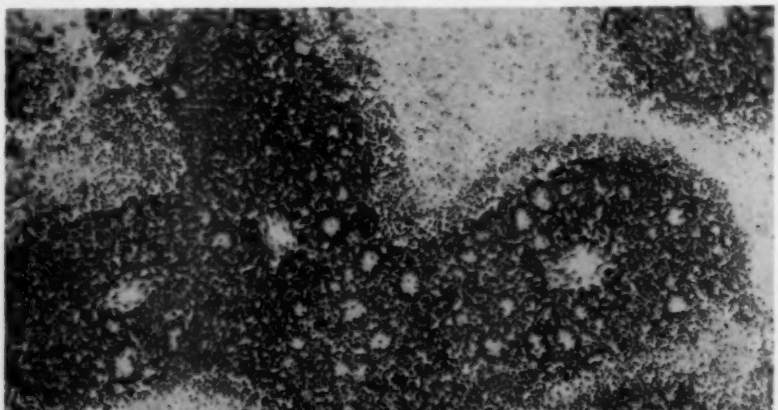

Fig. 7 (Reese and Straatsma). Retinoblastoma. Numerous neoplastic rosettes are seen in the cell masses surrounding blood vessels. (AFIP No. 147292, hematoxylin-eosin, ×115.)

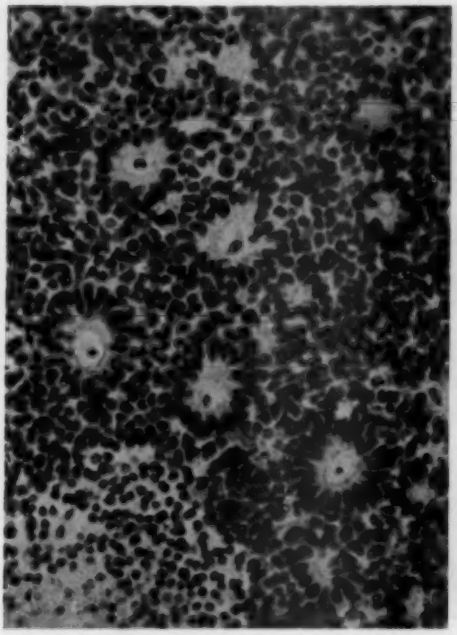

Fig. 8 (Reese and Straatsma). Retinoblastoma. Rosette structures are small and nearly round in all planes of section. (AFIP No. 147292, hematoxylin-eosin, ×305.)

Fig. 9 (Reese and Straatsma). Retinal dysplasia demonstrating general disorganization of the tissue morphology. (I.O.P.H. No. 7324, AFIP No. 846392, hematoxylin-eosin, ×115.)

may account for poor vision when the retinal fold spares the macular area. Gliosis may be extensive and occasionally necrosis of the retina is a feature.

A significant finding in retinal dysplasia is persistence of the primary vitreous. In all cases there is a plaque of fibrovascular tissue attached to the inner surface of the agenetic retina and bound to the posterior surface of the lens. The character and location of this tissue indicates that it is a persistence of the primary vitreous and is proof that the secondary vitreous has failed to form. The assumption is that the persistence of the primary vitreous, the failure of the secondary vitreous to form, and the dysplasia of the retina are all related in the development of this anomaly.

Thus far the pathologic features in common to all of these cases have been discussed. Other sporadic developmental ocular anomalies that may be seen in conjunction with retinal dysplasia are microphthalmos of variable and often slight degree, a shallow anterior chamber with posterior synechias, anterior synechias, and a fetal type filtration angle, and lens opacity that is usually mild in degree. Colobomatous anomalies involving the iris, choroid, and optic disc are not uncommon, and cystic retro-ocular structures are occasionally present. Even the optic nerve is involved in some cases and may show disruption of its architecture that is consistent with the appearance of atrophy.

The malformation of the filtration angle accounts for the not infrequent elevation of intraocular pressure. This may manifest itself as a form of acute glaucoma, or it may be apparent as a gradual ectasia of the globe (buphthalmos). A final feature which should be mentioned in the evolution of ocular pathology is the occurrence of hemorrhage that may arise anterior to the retina and lens, or develop in the subretinal space. In this series of cases hemorrhage in both areas has been encountered and is undoubtedly a feature influential in the retrograde ocular changes.

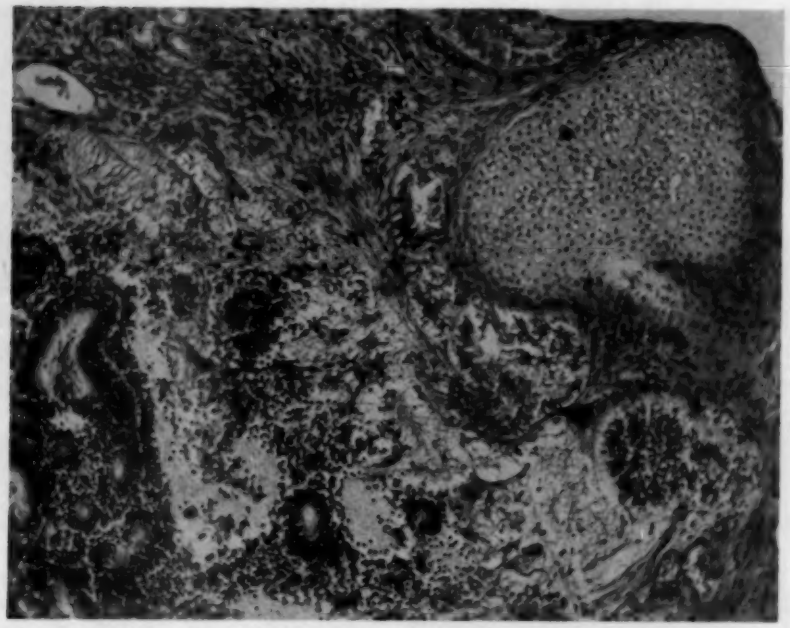

Fig. 10 (Reese and Straatsma). Dysplastic retinal tissue containing extensive gliosis, necrotic elements, and an area of cartilage. (AFIP No. 523225, hematoxylin-eosin, ×115.)

Fig. 11 (Reese and Straatsma). Fibrovascular remnants of the primary vitreous are located between the dysplastic retina and the cataractous lens. (AFIP No. 514013, hematoxylin-eosin, ×50.)

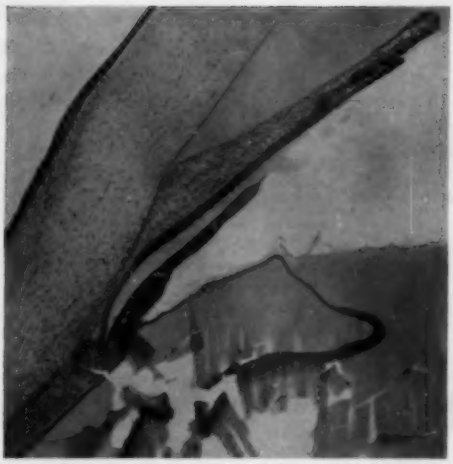

Fig. 12 (Reese and Straatsma). Retinal dysplasia. Elongated ciliary processes and an abnormal filtration angle are prominent features. (I.O.P.H. No. 7324, AFIP No. 846392, hematoxylin-eosin, ×50.)

B. Central nervous system pathology

Central nervous system abnormalities are characteristically associated with the ocular pathology of retinal dysplasia, and 13 patients in this series showed aberrant central nervous system development. Hydrocephalus was the primary defect in six patients, and six others showed severe mental retardation. Other anomalies encountered included encephalocele, meningocele, cerebral hypoplasia, cerebellar malformation, deformity of the brain stem, and the Arnold-Chiari alteration.

C. General system pathology

Many other general developmental defects were present in these patients. These defects involved every major system of the body and may be listed as follows:

Respiratory system (five patients affected). Aplasia of the left lung, unilobate left lung, bilobate right lung, atelectasis, and diaphragmatic defect with hernia.

Gastro-intestinal system (five patients affected). Pyloric stenosis, atresia of the duodenum, absence or hypoplasia of the gallbladder, bile duct atresia and hepatomegally, caecum mobile, abnormal rotation of the colon, and omphalocele.

Musculo-skeletal system (five patients affected). Polydactylism, cleft lip and palate, micrognathia, club foot, club hand, and hemivertebrae with scoliosis.

Cardiovascular system (three patients affected). Patent foramen ovale, septal defect, and bicuspid aortic valve.

Genito-urinary system (three patients affected). Cysts of the ovary, renal cysts,

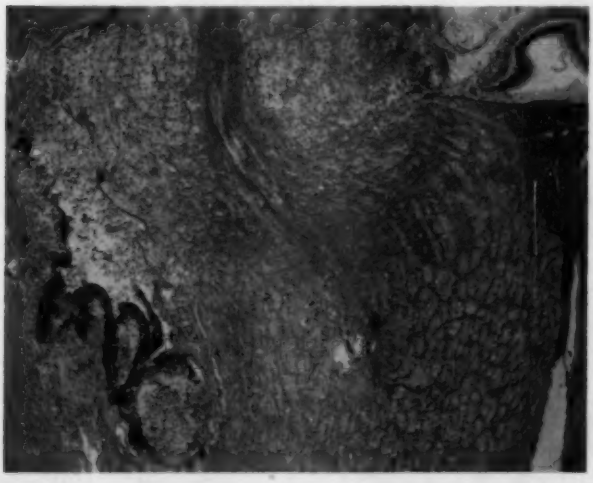

Fig. 13 (Reese and Straatsma). Retinal dysplasia with associated coloboma involving the optic disc and nerve. (AFIP No. 45389, hematoxylin-eosin, ×50.)

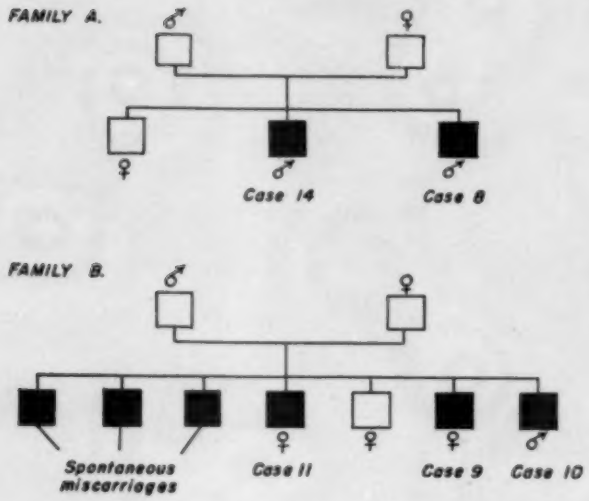

Fig. 14 (Reese and Straatsma). Two cases of retinal dysplasia occurred in Family A and three cases developed in Family B. The general history in both families was unremarkable and each couple had one normal child.

cryptorchidism, and phimosis.

Lymphatic-hematopoietic system (two patients affected). Myeloid metaplasia in the liver and thymus, acute splenic tumor, and multiple accessory spleens.

Endocrine system (one patient affected). Multiple accessory adrenal glands.

Discussion

Analysis of the cases in this report reveals that retinal dysplasia is a diffuse syndrome characterized by multiple congenital anomalies. The common feature in these collected cases is the ocular defect, and even this pathology may vary within broad limits. The most consistent feature of the ocular aberration is the abnormal retinal development that is associated with retinal rosettes.

A valid discussion should emphasize that even these retinal rosettes are not specific for retinal dysplasia. In fact, typical rosettes entirely analogous in appearance to those seen in retinal dysplasia may be produced experimentally by subjecting mice to anoxia in utero,[9] treating developing rats with X-radiation,[10] injecting minced embryonic ocular tissue from rats into the brain or cranial cavity of adult rats,[11] or simply inbreeding a predisposed strain of albino rats.[12] Retinal rosettes have also been noted in hanging drop cultures of isolated rat retina and in tissue cultures of isolated fetal rat eyes.[10] Tissue cultures of human fetal retinas have shown the pattern of rosette formation,[13] rosettes have been recorded in an ocular teratoma found in a human ovarian cyst,[14] and they have occurred in the retina secondary to radiation of the human fetus in utero.[15, 16]

This list of factors responsible for abnormal retinal development and rosette formation in both animals and humans indicates that this form of dysgenesis is a common form of aberrant retinal growth. In all probability any one of many insults to the developing retina may produce this distinctive form of tissue maldevelopment.

The etiology of retinal dysplasia in clinical cases is unknown, but the foregoing considerations suggest that it is the result of a diffuse disturbance at a critical point in development when the tissues are undergoing their most rapid differentiation. Current general concepts concerning developmental abnormalities imply that this insult may be due to a defective genetic mechanism, an environmental disturbance, or a combination of the two factors.[17] Several cases in this series of retinal dysplasia reported uterine bleeding during pregnancy, or polyhydramnios consistent with a disturbance in the environ-

ment of the developing organism. A genetic basis for retinal dysplasia is suggested by the occurrence of two or more cases in a single family. In this series, two families accounted for five of the cases.

Regardless of the factor or factors responsible for the aberrant ocular differentiation of retinal dysplasia, one might expect to encounter related malformations of lesser and greater degree. Clinical and pathologic material confirm this concept and demonstrate a broad and continuous spectrum of disease characterized by aberrant retina containing rosettes and persistence of the primary vitreous. This unbroken spectrum extends from the most severe forms of microphthalmos in which no type of retinal dysgenesis can be considered, through the range of retinal dysplasia to the cases of congenital retinal fold, and finally to simple persistent hyperplastic primary vitreous.[18]

Congenital retinal fold or retinal septum has been well described by Mann[19] and others who have noted the persistence of

TABLE 2

CONGENITAL RETINAL FOLD

Cases		
Histologically Confirmed	Clinically Diagnosed	
AFIP 568704	P.C.	P.H. Unit No. 1344958
131910	M.G.	P.H. Unit No. 230444
716054		
720586	D.G.	Children's Clinic No. 874
83124	H.G.	Children's Clinic No. 726
312149	J.L.	P.H. Unit No. 287332
633990		
270559		
36830		
90873		
115853		
152299		
163981		
318624		
46456		
199800		
295908		
501246		
526293		
653537		
IOPH 5918R		
6809R		
Total 22		5

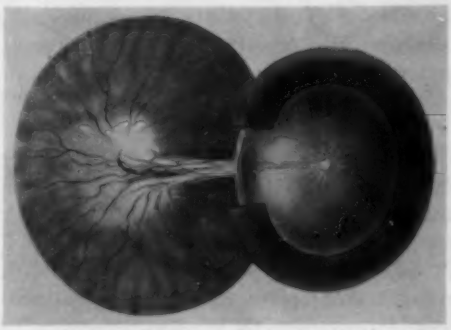

Fig. 15 (Reese and Straatsma). Retinal fold drawn from P. H. Unit No. 1344958. The clinical appearance of the fold and the retinal histology may simulate retinal dysplasia. However, retinal fold is not associated with abnormalities involving other body systems and distinction may be made on this basis.

fibrovascular tissue from the primary vitreous, the abnormal differentiation of the entire retina, and the retinal rosettes in the elevated retinal fold. Clinically, the retinal fold is usually seen as an elevated ridge extending from the optic disc to a plaque of vascularized tissue on the posterior lens surface. Abnormal vessels generally travel along the peak of this ridge. These patients usually have visual impairment related to disturbance of the macula or an over-all abnormal retinal development.

Our experience with congenital retinal fold includes 22 histologically confirmed cases and five cases clinically diagnosed (table 2). In these 27 cases there was no evidence of maldevelopment involving other body systems.

Although the microscopic picture of retinal dysplasia is definite, there are a number of conditions that may simulate the disease clinically. Therefore, it is in order to consider now the differential diagnosis. The ocular features of the disease must be distinguished from other congenital defects, metabolic disease, inflammation, retrolental fibroplasia, and neoplastic disorders. The variable appearance of retinal dysplasia may necessitate differentiation from congenital glaucoma, congenital cataract, retinal fold, and hyperplastic primary vitreous. Metabolic cataracts

associated with galactosuria, the ground-glass cornea of Hurler's syndrome (gargoylism), and the changes of inflammation may also pose differential considerations.

Retrolental fibroplasia, however, is particularly apt to mimic retinal dysplasia because of features common to the two diseases such as bilaterality, microphthalmos, and mental retardation. The confusion would probably be greatest in Grade V cicatricial retrolental fibroplasia where microphthalmos may be prominent, the iris-lens diaphragm is forward, secondary corneal changes are present, and glaucoma is frequent. Confusion may also exist in milder grades of retrolental fibroplasia where a fold or partial detachment is present.

Mental retardation has a higher than normal incidence in premature children and is perhaps associated with an even higher incidence in those premature children afflicted with retrolental fibroplasia. However, the characteristic sequence of prematurity, oxygen therapy, and progressive disease during the early weeks and months of life facilitates differentiation of retrolental fibroplasia from true retinal dysplasia.

An important differential is necessary between retinal dysplasia and retinoblastoma. Many examples of retinal fold, congenital retinal detachment, and persistent hyperplastic primary vitreous have been in eyes enucleated with the erroneous diagnosis of retinoblastoma. Significant differential points include the following: (1) microphthalmos, shallow anterior chamber, and cataractous changes are associated with dysplasia and allied conditions but are not seen in retinoblastoma; (2) dysplasias invariably present some degree of tissue adherent to the posterior surface of the lens; (3) retinoblastoma is characteristically seen as a creamy-white mass containing blood vessels and dispersed with chalky-white deposits at varying depths in the translucent tissue; (4) dysplasia is present at birth while retinoblastoma is appreciated only in the first year or so of life.

Summary

Retinal dysplasia is a diffuse developmental aberration characteristically affecting both eyes, the central nervous system, and other systems of the body, with indications of a familial trend. Of the 44 cases on which this report is based, 17 manifested the disease in its complete form terminating in death for 12 patients. The remainder of the cases in this series were incomplete or abortive forms showing ocular changes in the nature of retinal maldevelopments without associated general anomalies.

Clinically, the ocular malformations present with variable degrees of microphthalmos, a shallow anterior chamber, remnants of the pupillary membrane, and synechias which are responsible for an irregular bound-down pupil. There are mild cataractous changes but the prime feature is a white mass in the retrolental area. These eyes are subject to glaucoma and are prone to intraocular hemorrhage. Histologically, these ocular changes are related to a dysplasia of the retina associated with characteristic irregularly shaped rosettes, retinal detachment, and persistent elements of the primary vitreous. In addition, the filtration angle is generally fetal in type.

The etiology is unknown but clinical and experimental evidence indicate that retinal dysplasia is the nonspecific reaction of the developing retina to an environmental or genetic insult.

The ocular changes of retinal dysplasia are related to other congenital anomalies of the eye. A broad spectrum of disease is postulated extending from poorly differentiated extreme microphthalmos, through the degrees of retinal dysgenesis to persistent hyperplastic primary vitreous. Consideration is given to the differential diagnosis with particular regard to distinguishing among retinal dysplasia, retrolental fibroplasia, and retinoblastoma.

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STUDY OF AFFERENT ELECTRIC IMPULSES INDUCED BY INTRAOCULAR PRESSURE CHANGES*

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Recent investigations of effects of electric stimulation at various sites in the cat's diencephalon have provided evidence for occasional isolated intraocular pressure responses brought about by stimuli applied at ill-defined areas in the dorsal hypothalamus and ventral thalamus.[1,2] The nature of the efferent pathways and the mechanism of action by which the stimuli produce such rises or falls of the eye pressure elude analysis at present. However, when points in the ventral part of the hypothalamus are stimulated, intraocular pressure changes are usually accompanied by parallel or similar changes of the general blood pressure, variations in the state of the vascular bed in the ear auricle, and pupillary reactions. Here the involvement of sympathetic centers and pathways is conclusive. What significance could be attached to the experimental proof of centrally elicited efferent effects remains questionable.

The present study deals with the search for intraocular pressure receptors and affer-

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ent pathways of a nervous mechanism which may play a part in the regulation of the eye pressure. Claims that afferent discharges can be induced by intraocular pressure variations have been made in the past, but either the problem has been treated in a preliminary way as a side issue in the study of touch receptors of the cornea,[3] or the responses to intraocular pressure changes and to touch were not distinguished from each other.[4] Nevertheless, both types of investigations contain important information.

Materials and Methods

Thirty-seven young adult cats of both sexes, weighing from 2.1 to 3.9 kg., were either anesthetized with Chloralose (40 mg./kg.) or with sodium pentobarbital (30 mg./kg. + supplement) in 30 experiments, or were decerebrated under brief ether anesthesia (seven experiments). Six young Rhesus monkeys weighing about 2.0 kg. received intraperitoneal injection of sodium pentobarbital (approximately 45 mg./kg.). In all experiments the left femoral artery was cannulated for continuous recording of the blood pressure. A cannula in the left femoral vein allowed for administration of drugs, additional anesthetics, or 0.9-percent solution of sodium chloride. Tracheotomy was performed routinely in cats, and artificial respiration, when needed, was given by means of a Palmer pump.

In order to lead off afferent signals from ciliary nerves the posterior pole of one eye was exposed by the temporal approach similar to a Kroenlein procedure. The skin and temporal muscles were resected and the temporal wall of the bony orbit removed with rongeurs. Upon deflection of the severed temporal and superior recti muscles and rotation of the globe nasalward, the optic nerve came into view. The ciliary nerves and accompanying vessels course forward closely attached to the dural sheath of the optic nerve. The nerves were cautiously isolated under ×10 magnification of the Zeiss binocular otoscope and, in about a third of the experiments, were followed backward to their origin at the ciliary ganglion.

In the preparation of the nerves great care was exercised to avoid injury to accompanying or neighboring vessels. As a rule only the posterior temporal and superior ciliary nerves were prepared. The nasal and inferior branches, scarcely accessible with this technique, were explored in a few instances.

Usually from three to seven nerves were isolated for the examination. They were cut between the posterior pole of the eye and the ciliary ganglion and placed on fine, silver wire electrodes. In some instances, the branches were dissected to few fiber bundles. Instillation of light mineral oil in the operation area prevented drying of the dissected nerves.

The electric signals were amplified by means of a Grass AC pre-amplifier and monitored on one channel of an ETC dual channel oscilloscope with loud speaker. Photographic recordings were made with a Grass camera. Prior to the recording of impulse activity of the nerves, two 27-gauge needles were inserted into the anterior chamber at the limbus and arranged to lie parallel to each other and to the iris. Both needles had been fixed to the ends of No. 10 polyethylene tubing and the system filled with 0.9-percent solution of sodium chloride with careful removal of air bubbles.

The eye pressure changes were transmitted through one needle with the attached polyethylene tubing to a Statham transducer and recorded both on a Sanborn polyviso recorder and on the second channel of the cathode-ray oscilloscope. The second needle was connected, through the fine tubing, with a syringe microburet filled with 0.9-percent solution of sodium chloride to serve for the induction or withdrawal of small quantities of fluid into or from the anterior chamber. If the condition of the preparation permitted prolongation of the experiment, the same procedure was applied to the second eye.

Graded Fry test hairs and nylon threads or pointed cotton applicators were used

to test for electric responses to touch stimuli applied to the cornea or sclera. Finally, in eight cats and four monkeys the contents of the orbit were fixed in formalin, subjected to Christensen's silver technique, and examined under the stereomicroscope. Other preparations were dissected in the fresh state. In several instances the nerves from which pressure-induced impulse activity was obtained had been marked with thread loops. From four cat and two monkey preparations pieces of long and short ciliary nerves were removed, imbedded in paraffin, and cut in five-micron sections perpendicular to the length axis. The diameter of the fibers they contained, their myelination, and the relation of fine to thick elements were estimated.

Results

Eight of the 37 cat preparations showed electric responses to changes of the intraocular pressure as well as to touch; the records of these experiments could be satisfactorily analyzed. In 15 preparations afferent impulses were elicited by touch stimuli only. In seven animals spontaneous electric activity was observed, but the pressure-induced signals were too erratic and short-lasting for interpretation of the films. The eight remaining preparations did not exhibit any afferent discharges. Two of the six experiments on monkeys permitted the study of pressure-evoked potentials in the ciliary nerves. The evaluation of the records is limited, then, to eight experiments on cats and two on monkeys, although several of the excluded preparations provided some pertinent information.

The impulse frequencies were estimated by counting all spikes, although of different heights, in portions of the film, and plotting the counts against time in seconds. The frequencies were measured in the records of two preparations in which a single unit was firing. All graphs also contain the tracings of the intraocular pressure changes in their time relationship to the discharge frequency variations.

Spontaneous electric activity recorded at various intraocular pressure levels in beginning of experiment

The average spontaneous frequency of afferent impulses varied from one preparation to the next in a range of from three to 40 spikes per second; such afferent signals were absent in one pressure-sensitive monkey preparation. The starting intraocular pressure in these experiments varied from 10 to 20 mm. Hg. Spontaneous discharge frequency appeared to be independent of the individual intraocular pressure level, the type of anesthesia or decerebration procedure, the age of the animal, and the condition of the preparation as judged by temperature and blood pressure. In some experiments afferent signals were obtained from one or two isolated branches only; in others all prepared nerves conducted the impulses. The discharge spikes of equal amplitude followed one another at fairly regular intervals. Figure 1 illustrates the uniform firing of a single unit. In other nerves of the same preparation or in different experiments spikes of various amplitudes and frequency signified activity of two or several units (fig. 2).

Electric responses to rises of the intraocular pressure of varying increments and speeds

In the selected group of preparations an intraocular pressure rise from a starting or a low level to a higher one was achieved rather rapidly by stepwise injection of small fluid volumes or by infusion of such quantities at a slow rate. Under both conditions the impulse frequency in the ciliary nerves increased in a manner roughly proportional to the pressure increments (fig. 3), but in no case could strict linearity be established between intraocular pressure rises and firing rates. There is reason to believe that the poor correlation between the two functions can be ascribed in part to sluggish recording of the intraocular pressure. The spike frequency either increased, almost synchronously with the pressure rise (fig. 4), or responded to

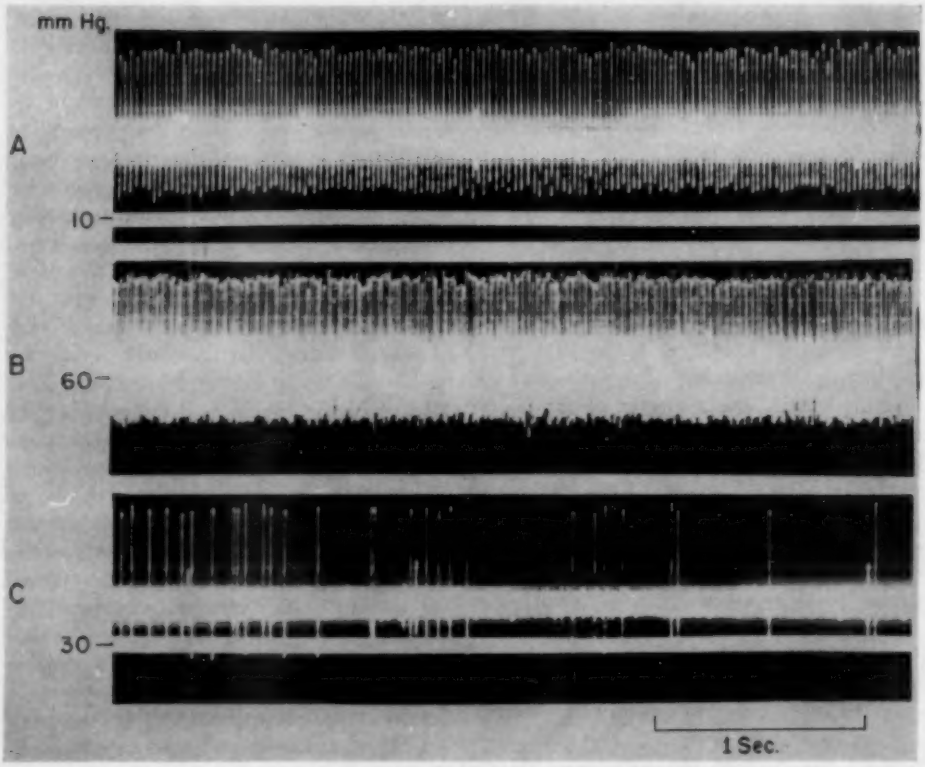

Fig 1 (von Sallmann, et al.). *Electric activity of a single unit in relation to intraocular pressure.*
(A) Spontaneous firing is recorded at the pressure level of 10 mm. Hg.
(B) Increase of spike frequency accompanies the rise of intraocular pressure to 60 mm. Hg.
(C) A decrease of firing rate is brought about by lowering the intraocular pressure from 60 to 30 mm. Hg. The activity is irregular with brief intervals of silence. (Cat 189.)

the stimulus with a delay which could be as long as 15 seconds (fig. 5). Sometimes the impulse frequencies attained their maximal value before the pressure peak was reached, but in other instances the sequence was reversed (fig. 6).

The most sensitive pressure range at which impulse discharges increased in response to small pressure increments was observed in two cats at intraocular pressure readings between 10 and 20 mm. Hg (figs. 2, 3, and 4) and in other preparations between 20 and 50 mm. Hg (figs. 1 and 6). Here a rise of intraocular pressure of only a few mm. effected the increase of the discharge rate. In the monkey preparation without spontaneous activity small pressure increases evoked potentials at an intraocular pressure level of 10 mm. When the intraocular pressure was stepped up rapidly to 30 and 40 mm. Hg a similar and almost synchronous increase of the firing rate resulted. The second monkey responded in an irregular manner to pressure rises above a 60 mm. Hg pressure level.

Parts of records which showed an approximately synchronous increase of the intraocular pressure and the spike frequency were selected for further analysis. In five instances the intraocular pressure values were plotted against spike frequency at several points during a pressure rise. The slope of the line thus obtained expresses the

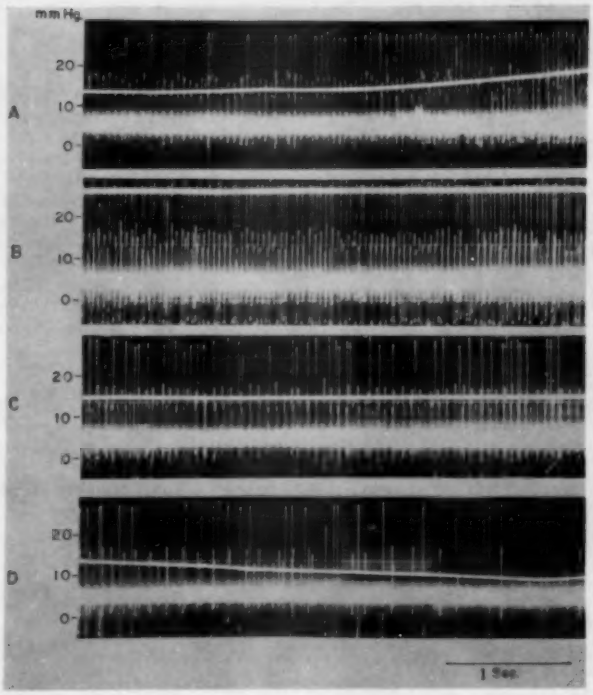

Fig. 2 (von Sallmann, et al.). *Electric activity of several units in relation to intraocular pressure.*

Small pressure variations within the range of 10 to 20 mm. Hg cause marked changes in the spike rate. This is illustrated in (A) (B) (C) and (D) for various increases and decreases of the intraocular pressure. (Cat 195.)

change of impulse frequency per unit of pressure rise. The values determined in this manner ranged from 0.2 to 2.5 impulses per second per mm. Hg.

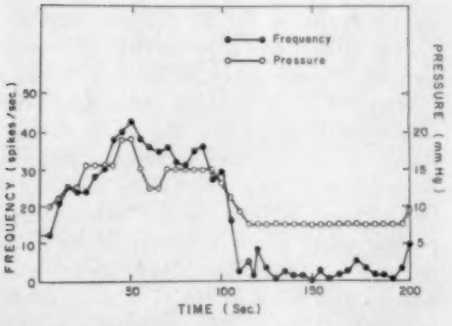

Fig. 3 (von Sallmann, et al.). The graph shows rough proportionality of intraocular pressure and frequency changes at the pressure range from 10 to 20 mm. Hg. A long postexcitatory depression follows a pressure fall of only 8.0 mm. Hg. (Cat 197.)

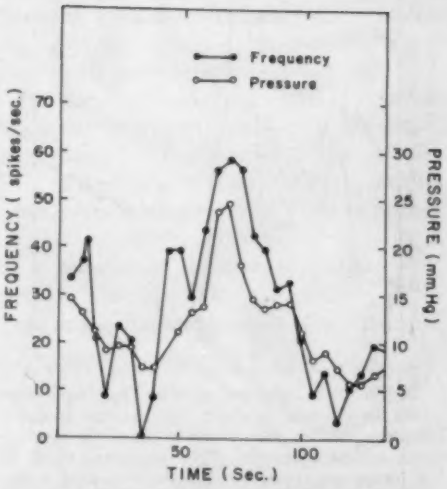

Fig. 4 (von Sallmann, et al.). The graph depicts an almost synchronous relationship between pressure and frequency changes. The data are obtained from the experiment recorded in Figure 2.

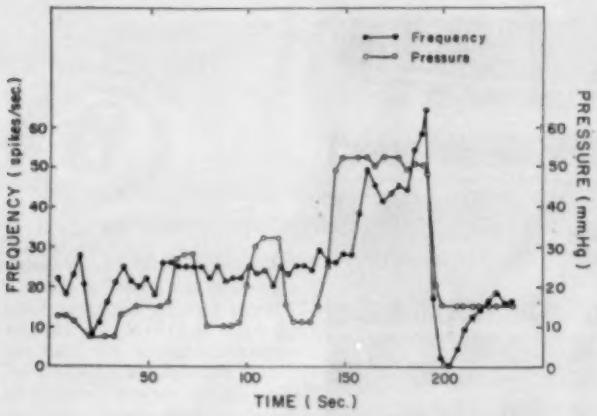

Fig. 5 (von Sallmann, et al.). The graph exemplifies a delayed electric response to the elevation of intraocular pressure. Pressure variations between 10 and 30 mm. Hg do not affect the spontaneous activity. By raising the pressure to 50 mm. Hg the impulse frequency increases with a delay of about 15 seconds. The rapid fall from 50 to 15 mm. Hg interrupts the firing only briefly. The frequency returns to its control value within 15 seconds.

When the increased intraocular pressure was kept constant for 30 to 40 seconds, high impulse frequency was fairly well sustained, but small variations of the firing rate occurred during this period (fig. 7). A slight decrease of impulse frequency after the initial maximal value was reached may be accounted for by an adaptation phenomenon; however, the pressure plateaus were not extended sufficiently long to prove this point.

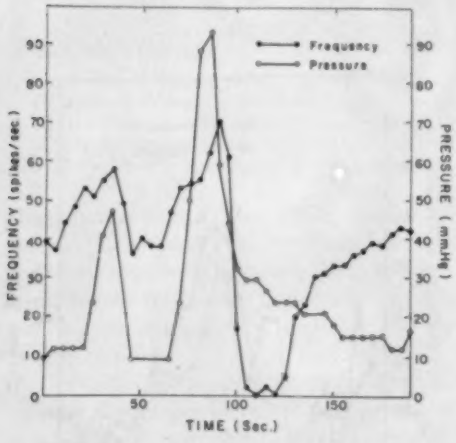

Fig. 6 (von Sallmann, et al.). The graph represents an instance in which the maximal frequency response occurs five seconds after the pressure peak has been reached. The subsequent rapid fall of intraocular pressure is associated with a steep decline of impulse frequency and is followed by a pause of approximately 20 seconds' duration. The frequency returns to its control value within 70 seconds. (Cat 189.)

Electric responses to falls of the intraocular pressure

A sudden or gradual drop of the intraocular pressure was accompanied regularly by a decrease of impulse frequency. When the pressure dropped slowly from 25 to 8.0 mm. Hg over a period of 40 seconds the firing rate decreased from 60 spikes per second to five spikes per second. A sudden fall in the intraocular pressure from a level of 100 mm. Hg to 30 mm. Hg was reflected in a steep, almost synchronous, decrease of the frequency. Then the firing subsided almost completely for 20 seconds (fig. 6). Figure 3 illustrates a postexcitatory depression of approximately 90 seconds duration following a decrease of the intraocular pressure from 15 to 8.0 mm. Hg. In another instance, a fall of the intraocular pressure from 50 to 15 mm. Hg briefly interrupted the discharge activity but did not result in a postexcitatory pause. Recovery of the firing rate to the characteristic level of spontaneous activity took place within 15 seconds in one preparation (fig. 5) but required in another experiment about 70 seconds (fig. 6) beginning from the end of the postexcitatory depression which had lasted 20 seconds. The unequivocal association of pressure falls of

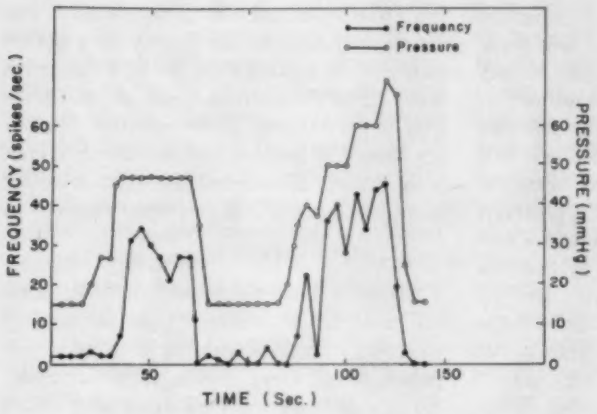

Fig. 7 (von Sallmann, et al.). The graph demonstrates small variations of impulse frequency during a period of sustained elevated intraocular pressure. (Cat 210.)

various rates and various extent with a parallel decrease in the discharge rate could be shown in the same nerve repeatedly. It presents the most often observed characteristic electric event in this experimental series.

Electric responses to touch as compared to pressure-evoked afferent signals

The effect of touching the cornea on electric discharges in ciliary nerves has been elaborately investigated by S. S. Tower.[3] In the present study the responses to touch were not followed systematically; that is, the dependence of impulse rate on the intensity of stimuli was not recorded and the examination of circumscribed areas of the cornea in a point-to-point manner was not intended. Responses to corneal touch are signified by bursts of spikes and rapid adaptation of the signals. They share then the characteristics of touch receptors elsewhere, especially in the skin.

In the present work, touch-evoked short-lived bursts of impulses were elicited more frequently than pressure-induced changes of spike frequency. In some preparations the same nerve branches seem to conduct both touch and pressure-induced activities. In other preparations touch responses could not be detected in nerves which showed increased firing rate to pressure rise, but more frequently the opposite was true: pressure changes were ineffective in producing increased electric activity in the tested nerves, whereas, touch stimuli were adequate to evoke the typical bursts of spikes.

In our series of experiments touch applied to the limbus area and a one-mm. broad zone of the peripheral cornea produced bursts of impulses more frequently and in response to stimuli of lower intensity than was the case when an inner ring zone or a central area of the cornea was stimulated. This marked difference between the limbus zone and the main part of the cornea was observed in most preparations.

On the other hand, S. S. Tower obtained the lowest threshold and highest frequency of responses at a central area. The discrepancy in these observations may lie in the difference of technique. S. S. Tower trimmed off the conjunctiva and sewed a fringe of it to a ring fitting the corneal margin. It is possible that this fixation procedure of the globe made the limbus area less accessible.

Anatomic observations on posterior ciliary nerves

Anatomic studies on the orbital content of the cat confirmed the observations of Kermit Christensen[8] with regard to the great variability of the relationship of long and short ciliary nerves to each other. Taking the

location of the long ciliary nerves in the horizontal plane of the globe and their topographic association with the long ciliary arteries as the criterion of identification, only two of these nerves could be observed in individual preparations; sometimes they were subdivided into two or three branches.

In frontal sections through the posterior half of the eye they were seen to course forward in the sclera accompanied by two fine venous branches and the long ciliary arteries. When the nerves were followed backward to the ciliary ganglion, fusion with branches of short ciliary nerves frequently took place.

In the examined anatomic preparations the long ciliary nerves appeared to terminate in the ganglion either after joining with one of the main bundles of the short nerves or as separate branches. Suggestive evidence has been obtained that a fine nerve branching off from one of the short ciliary nerves peripheral to the ganglion contains afferent pathways in addition to sympathetic fibers. The latter have been identified by electric stimulation which produces dilatation of the pupil.

Of the two main nerve trunks emerging from the anterior pole of the ciliary ganglion the superior lateral one divided progressively into from six to 12 branches, which entered the sclera around the optic nerve in the temporal and superior aspect of the globe. The nasal inferior trunk was slightly thinner and gave off a smaller number of branches to the sclera and the nasal inferior aspect of the globe. All these anatomic observations applied in a similar way to the ciliary nerves of Rhesus monkeys. The long ciliary nerves in this species also seemed to originate from the ciliary ganglion, occasionally without fusion with branches of the short ciliary nerve.

The microscopic examination of paraffin imbedded nerves in cross sections showed medullated fibers of different diameters. In the long ciliary nerves of cats the fine fibers measured about two microns and the thick fibers five microns. They varied in diameter from five to six microns in the monkey. The main component of the short ciliary nerves consisted of medullated fibers of diameters from 1.5 to 2.0 microns in the cat and from four to six microns in the monkey. Shrinkage caused by fixation and imbedding has not been studied. Nonmedullated fibers have not been detected with the employed methods.

Discussion

Sarah S. Tower published, in 1940, a remarkable article entitled "Unit for sensory receptors in cornea with notes on nerve impulses from sclera, iris, and lens." Spontaneous discharges led off from long ciliary nerves were increased in rate by injection of Ringer solution into the anterior and posterior chamber. The very large impulses were stated to be definitely not of a corneal origin. The preliminary nature of the pressure experiments is indicated in the summary in which the author refers to "some notes on afferent impulses in response to increases of the intraocular pressure."

In the same year W. Dieter[4] delivered at the meeting of the German Ophthalmological Society in Heidelberg a brief report on action potentials in short ciliary nerves which resulted from increases of the intraocular pressure produced either by pressing against the cornea with a dynamometer or by injection of fluid into the anterior chamber through a Leber cannula. Dieter concluded that afferent impulses originating in pain receptors of the cornea or iris or muscle action potentials could not be incriminated as the cause of the observed electric activity; no reference was made as to whether or not touch receptors were involved in the electric phenomena.

Besides these fragmentary reports, the connection of intraocular pressure changes with afferent impulses has not been investigated, to the best of our knowledge, although the importance of such information has been stressed.[2]

In the present study the records of about one fourth of the experiments on cats and

monkeys were interpreted in favor of the existence of slow adapting receptors in the eye which reacted to pressure changes of low intensity. The range of the intraocular pressure of highest sensitivity for such stimuli extended from a level of 10 to one of 30 mm. Hg, values which encompass the pressure levels of the normal eye.

Afferent impulses caused by intraocular pressure changes and by touch were conducted by both long and short ciliary nerves. The fairly well sustained increase of impulse frequency for the duration of the elevated intraocular pressure and the rapid fall of electric activity upon a sudden drop of intraocular pressure sometimes followed by a postexcitatory depression, resemble the nervous discharges so extensively studied and classically described for the carotid sinus nerve by Bronk and Stella[6, 7] and Landgren.[8] Pulsatile intraocular pressure fluctuations did not give rise to changes in the electric potentials, an observation similar to that on the isolated carotid sinus. It is not known where the intraocular signalling mechanism is located, and whether the arborizing axons terminating in the chamber angle[9–11] can be considered as pressure receptors.

The behavior of afferent impulses to touch were not made a part of systematic investigation in the present study, since S. S. Tower's work has clarified this relationship, but the difference between the rapidly adapting touch receptors and those which respond to intraocular pressure rises confirmed the observations of Tower. Our findings deviate from hers only in the location of the most sensitive part of the cornea to touch, which, in this study, proved to be the corneal-sclera junction.

It is not understood why the majority of preparations did not exhibit a spontaneous electric activity in any of the tested ciliary nerves, even when the preparations seemed to be in excellent condition. Temperature or drying effects, and injury to the vascular supply could be excluded as possible causes. For these reasons it appears premature to draw conclusions as to the physiologic significance of the observed afferent impulses. It is readily admitted that in this study merely informative data have been collected and that a quantitative evaluation of the connection between intraocular pressure variations and changes of the frequency of afferent impulses must await further refinement of methodical procedures and the continuation of the experiments with a modified technique.

The anatomic studies suggest that fifth nerve fibers course not only in the long ciliary nerves but are present also in the short ciliary branches. The difference of fiber diameters in the various nerves requires further study.

Summary

1. Potential changes were led off from posterior ciliary nerves of cats and monkeys, recorded, and photographed to study the effect of intraocular pressure rises and falls on the electric activity in these nerves. The effects of touch stimuli applied to the cornea on action potentials were examined as a side issue.

2. Spontaneous discharges and increased sustained impulse frequency in response to intraocular pressure rises were observed in about one fourth of the preparations. Both short and long ciliary nerves occasionally conducted the afferent impulses. Types of anesthesia or decerebration procedures or the condition of the preparation did not noticeably influence the electric phenomena.

3. The recorded spontaneous activity in cats and monkeys varied from three to 40 spikes per second and was absent in one pressure-sensitive monkey preparation. The highest pressure-induced impulse rate of 95 spikes per second concurred with an intraocular pressure rise to 100 mm. Hg.

4. In suitable preparations the tracings of impulse frequencies and of intraocular pressure changes roughly paralleled each other, inasmuch as intraocular pressure rises were accompanied by an increase of the firing rate.

The change of frequency per unit pressure rise was estimated to range from 0.5 to 2.5 impulses per second and mm. Hg.

5. The sensitivity of the intraocular signalling mechanism to pressure changes excelled in a physiologic range of the intraocular pressure (between 10 and 30 mm. Hg). Here, intraocular pressure changes of a few millimeters influenced the discharge frequency.

6. The essentially sustained character of the high discharge rate when the elevated intraocular pressure was kept constant and the close association between slow or sudden falls of the intraocular pressure and a corresponding decrease of firing rates sometimes leading to a postexcitatory pause resemble the phenomena extensively studied on carotid sinus pressure receptors.

7. Information collected in the reported experiments supports the view that the eye possesses slowly adapting receptors of a low threshold for slight changes of the intraocular pressure in a physiologic range. The large number of experiments with negative results remains unexplained.

Ophthalmology Branch (14).

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RETRACTION OF SCLERAL WOUND EDGES*

As a fistulizing procedure for glaucoma

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This paper presents a new method for performing a filtration operation for glaucoma. A fistula is produced by causing an ab externo scleral incision, made as for peripheral iridectomy, to gape by application of a galvanocautery superficially to the wound edges. The wound edges separate from 0.5 to 1.0 mm. with scleral contraction due to the heat of the cautery. The separation is greater on the external aspect of the wound than on the internal. Following application of the cautery, a peripheral iridectomy is done to prevent iris prolapse and plugging of the wound by iris. Filtration results in a high percentage of eyes.

The operation was developed after en-

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countering several filtering cicatrices following peripheral iridectomy for glaucoma during the first few months of 1956. The only variation in technique, during that time, had been application of a Hildreth cautery along the line of the prospective incision for purposes of hemostasis. Prior to this, filtration had been extremely rare. The filtering cicatrices seemed to be best explained by a slight retraction of the wound edges resulting from scleral shrinkage caused by the cautery. Scleral shrinkage following application of a cautery to sclera is well known and has been studied in some detail by Scheie and Jerome.[1] A less likely explanation was a disturbance in healing properties of cauterized sclera. The fact that filtration occurred was surprising because many ophthalmic surgeons have cautioned against the use of cautery, even for control of bleeding, when performing a filtration operation.

The cicatrices were rather flat and diffuse. Most of them resembled those seen after iridencleisis rather than the foamy, polycystic type of cicatrix which follows corneoscleral trephination. The appearance of the eyes was so excellent and they showed so little mutilation that it seemed reasonable to pursue the method, with some modification, as a filtration procedure.

The operation which was evolved is similar to that of Preziosi,[2] although the technique and the rationale are different. Both are filtration procedures but Preziosi's operation involves entering the angle of the anterior chamber with a galvanocautery thereby causing a fistula; while, in the operation being described in this paper, a fistula is created by causing a scleral incision to gape through superficial application of a cautery to its edges. It is emphasized that the cautery is applied only superficially to the lips of the scleral incision and that the chief difference between the procedures lies in the technique of using the cautery.

In the Preziosi operation a fistula is created by entering the anterior chamber with a cautery while in the procedure described in this paper the cautery only indirectly caused a fistula. A scratch incision is made into the angle of the anterior chamber with a scalpel. The incision is directed perpendicular to the surface of the sclera about one mm. behind the limbus. Because the wound edges are perpendicular they separate to form a cleft when the sclera contracts because of the cautery. The advantages from the standpoints of simplicity and safety would seem to accrue to the procedure in which the cautery does not enter the anterior chamber.

Technique

The operation is done under local anesthesia with facial akinesia. Anesthesia is obtained by conjunctival instillations of loca. anesthetic plus a retrobulbar block of the ciliary nerves. A lid speculum is placed and a superior rectus suture is inserted (fig. 1). The conjunctiva and Tenon's capsule are ballooned outward over the third of the globe at the operative site by the injection of procaine HCl (fig. 2). The conjunctiva and Tenon's capsule are incised, usually in the upper or lower temporal quadrant depending upon whether the operation is being done at the 12- or 6-oclock meridian, directly down to the sclera about seven mm. from the limbus (fig. 3). The blade of a scissors is in-

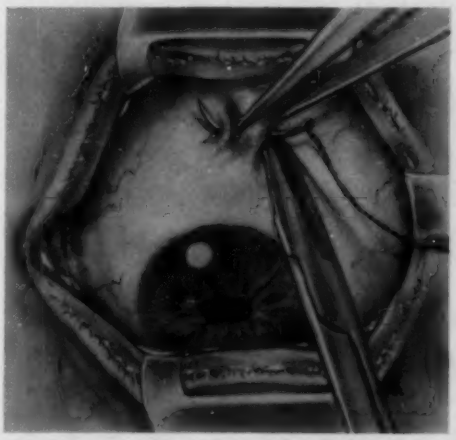

Fig. 1 (Scheie). Insertion of superior rectus suture.

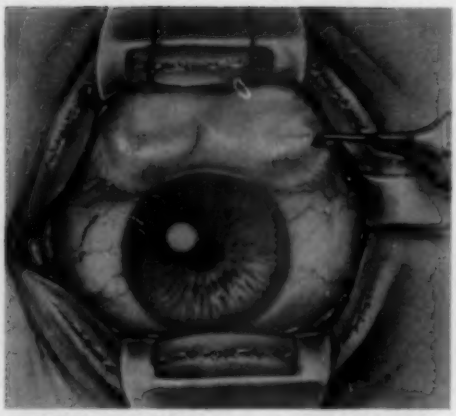

Fig. 2 (Scheie). Injection of Procaine HCl into conjunctiva and Tenon's capsule.

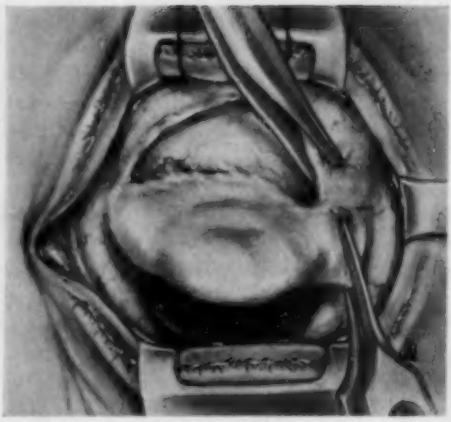

Fig. 4 (Scheie). Conjunctiva and Tenon's capsule reflected to the limbus.

serted between Tenon's capsule and the sclera and the incision is enlarged parallel to the limbus. Both Tenon's capsule and the conjunctiva are cut simultaneously. This large flap, of both layers, is then reflected to the limbus (fig. 4). The cornea is not split.

A series of applications of a Hildreth cautery is made to the sclera on a line parallel with and about one mm. back of the limbus (fig. 5). A scratch incision is made through the cauterized area, perpendicular to the surface of the sclera, to enter the angle of the anterior chamber as for peripheral iridectomy (fig. 6). The Hildreth cautery is again applied to the sclera over the lips of the incision to cause retraction of the wound edges of at least one mm. (fig. 7).

The posterior lip is usually cauterized more extensively than the anterior because it is more accessible. In eyes with wide open angles, aqueous usually escapes during application of the cautery rendering the cautery less effective and the field must be kept as dry as possible.

Peripheral iridectomy is always done upon completion of cauterization. In most in-

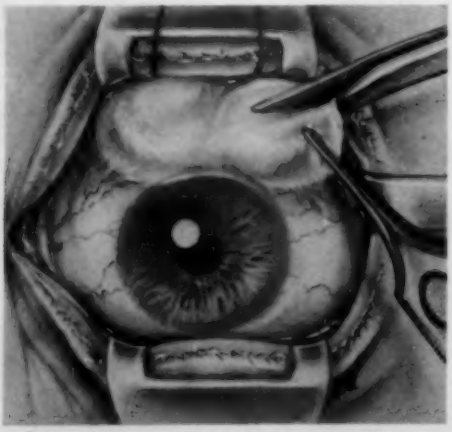

Fig. 3 (Scheie). Incision of conjunctiva and Tenon's capsule.

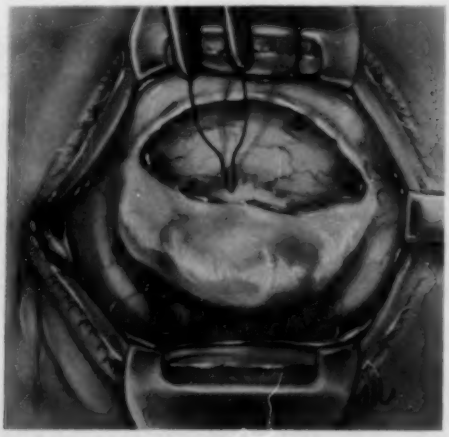

Fig. 5 (Scheie). Application of Hildreth cautery to line of incision.

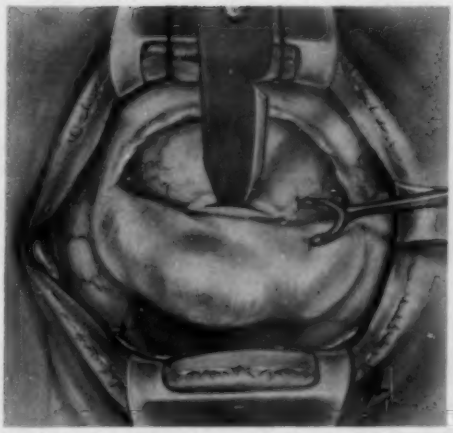

Fig. 6 (Scheie). Ab externo incision perpendicular to sclera one mm. behind the limbus.

Fig. 8 (Scheie). Prolapse of iris.

stances this is easily done because as the wound gapes from cautery, the iris ordinarily prolapses (fig. 8). However, when this does not occur, it usually can be made to do so by gentle pressure on the posterior lips of the wound. Occasionally, especially in eyes with wide angles, it may be necessary to enter the chamber with a forceps to withdraw the root of the iris.

Following iridectomy, the iris is replaced to free the peripheral coloboma. The incision in conjunctiva and Tenon's capsule is then closed by a continuous 6-0 catgut suture (fig. 10). Care is taken to close both Tenon's capsule and the conjunctiva as separate layers. No medication is instilled. Only the operated eye is patched. Reaction is slight and mydriatics usually are unnecessary postoperatively.

Presentation of data

The operation was performed upon 41 eyes of 30 patients (tables 1 and 2). Data on three of the eyes were contributed by

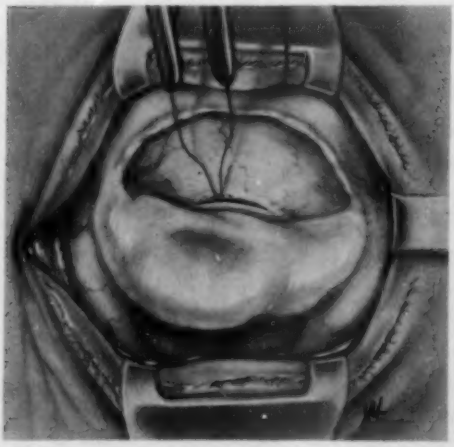

Fig. 7 (Scheie). Application of cautery to lips of scleral incision with gaping of wound.

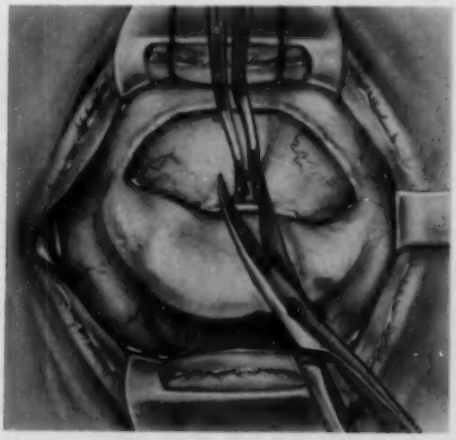

Fig. 9 (Scheie). Iris root grasped for peripheral iridectomy.

TABLE 1

SURVEY OF CASES PRESENTED

No.	Age	Sex	Race	Eye	Glaucoma			Tension (mm. Hg Schiøtz)	Date of Operation	Results			Post-operative Tension (mm. Hg. Schiøtz)
					Type	Optic Nerve	Fields			Controlled (normotensive)	Controlled with Hypotony	Uncontrolled	
1	48	F	W	OD	Narrow angle (chronic non-congestive)	Normal	Normal	Varied 35 to 62	7/24/56	X			17
				OS	Narrow angle (chronic non-congestive)	Normal	Normal	Varied 35 to 62	7/17/56	X			20
2	47	F	W	OD	Narrow angle (acute)	Normal	Normal	62+	7/24/56	X			12
				OS	Narrow angle (acute)	Normal	Normal	62+	7/25/56	X			17
3	43	F	W	OD	Narrow angle (chronic non-congestive)	Normal	Normal	26	8/ 4/56	X			24
4	46	F	W	OD	Narrow angle (acute)	Early optic atrophy	Moderately constricted	62	11/ 2/56	X			17
5	70	M	W	OS	Chronic simple (angle open)	Moderate cupping	Superior arcuate defect	40	11/13/56	X			27
6	75	F	W	OD	Chronic simple (narrow angle)	Marked cupping	Nasal constriction	46	4/18/57			X	35
				OS	Chronic simple (angle narrow)	Marked cupping	Nasal contriction	46	11/13/56		X		Less than 10
7	74	F	W	OS	Narrow angle (congestive chronic)	Atrophy and cupping	Marked concentric	79	11/20/56		X		Less than 10
8	80	M	W	OD	Chronic simple (angle narrow)	Marked cupping	Marked Nasal loss	46	11/27/56	X			20
				OS	Chronic simple (angle narrow)	Marked cupping	Marked nasal loss	40	7/12/57	X			17
9	59	M	W	OD	Chronic simple (angle narrow)	Normal	Normal	35	1/ 4/57	X			22
				OS	Chronic simple (angle narrow)	Marked cupping	Residual field	40	11/30/56			X	35

TABLE 1—*Continued*

TABLE 1—*Continued*

No.	Age	Sex	Race	Eye	Glaucoma			Tension (mm. Hg. Schiøtz)	Date of operation	Results			Post-operative Tension (mm. Hg. Schiøtz)
					Type	Optic Nerve	Fields			Controlled (normotensive)	Controlled with Hypotony	Uncontrolled	
10	78	M	W	OD	Chronic simple (angle wide open)	Moderate cupping	Roenne step	40	1/ 4/57	X			17
				OS	Chronic simple (angle wide open)	Early cupping	Normal	46	1/29/57	X			17
11	65	M	W	OS	Chronic simple (angle narrow)	Normal	Normal	40	1/ 8/57	X			22
12	64	F	W	OD	Chronic simple (angle narrow)	Marked cupping	Marked nasal loss	53	1/ 8/57		X		Less than 10
				OS	Chronic simple (angle narrow)	Marked cupping	Roene step	53	1/15/57		X		Less than 10
13	67	F	W	OD	Chronic simple (angle narrow)	Normal	Normal	40	1/15/57			X	35
				OS	Chronic simple (angle narrow)	Normal	Normal	40	1/25/57	X			20
14	79	M	W	OS	Chronic simple (angle open)	Marked cupping	Residual	46	1/17/57			X	40
15	56	F	N	OS	Chronic simple (angle open)	Marked cupping	Residual	46	2/ 7/57	X			17
16	60	M	W	OD	Narrow angle (chronic non-congestive)	Marked cupping	Residual	53	3/12/57		X		Less than 10
17	47	F	W	OD	Chronic simple (angle narrow)	Moderate cupping	Enlarged blind spot	40	3/19/57		X		10
				OS	Chronic simple (angle narrow)	Moderate cupping	Enlarged blind spot	40	3/12/57		X		10
18	51	M	W	OD	Narrow angle (chronic non-congestive)	Marked cupping	Residual	40	3/22/57		X		Less than 10
19	50	F	W	OS	Narrow angle (chronic congestive)	Marked cupping	Residual	83+	4/19/57	X			20

TABLE 1—*Continued*

No.	Age	Sex	Race	Eye	Glaucoma			Tension (mm. (Hg. Schiøtz)	Date of operation	Results			Post-operative Tension (mm. Hg. Schiøtz)
					Type	Optic Nerve	Fields			Controlled (normotensive)	Controlled with Hypotony	Uncontrolled	
20	75	F	W	OS	Chronic simple (angle narrow)	Early cupping	Baring of blind spot	53	4/26/57			X	30
21	65	M	W	OD	Chronic simple (angle wide open)	Normal	Normal	35	4/26/57	X			20
22	54	M	W	OD	Chronic simple (angle open)	Marked cupping	Marked loss	35	5/ 3/57		X		10
23	42	M	N	OS	Chronic simple	Marked cupping	Residual temporal island	40	5/10/57	X			23
24	72	F	W	OD	Narrow angle (acute)	Normal	Normal	83	5/22/57	X			17
25	63	F	W	OD	Narrow angle (acute)	Pale	Markedly contracted	80	6/ 1/57	X			20
26	37	M	W	OS	Chronic simple (angle wide open)	Marked cupping	Marked loss	40	6/ 3/57	X			15
27	68	M	W	OD	Chronic (narrow angle)	Marked cupping	Residual	42	6/ 3/57	X			26
28	67	M	W	OD	Chronic simple (angle narrow)	Normal	Normal	53	7/20/57			X	40
				OS	Chronic simple (angle narrow)	Moderate cupping	Inferior arcuate	53	6/ 8/57	X			17
29	50	F	N	OS	Chronic simple (angle open)	Moderate cupping	Residual	60+	7/ 9/57	X			22
30	57	F	W	OD	Narrow angle (chronic non-congestive)	Marked cupping	Marked loss	32	7/20/57	X			20
				OS	Narrow angle (chronic non-congestive)	Marked cupping	Marked loss	30	7/30/57	X			15

TABLE 2

SUMMARY OF RESULTS OBTAINED FROM PERFORMING PERIPHERAL IRIDECTOMY WITH CAUTERY ON 41 EYES WITH PRIMARY GLAUCOMA

Type of Glaucoma		Controlled (Normo-Tensive)	Controlled with Hypotony	Uncontrolled
Narrow Angle				
Acute	5	5	0	
Chronic	9			
congestive (2)		1	1	
noncongestive (7)		5	2	
Total Narrow Angle	14			
Chronic Simple				
Angle narrow	17	7	5	5
Angle open	10	8	1	1
Total Chronic Simple	27			
Total	*41*	*26*	*9*	*6*

Dr. Gaylord W. Ojers who operated upon them in his private practice. All patients have been followed from two to 14 months. All eyes had primary glaucoma associated with diminished facility of outflow of aqueous. Twenty-seven eyes had chronic simple glaucoma. The angles were nicely open in 10 eyes and very narrow in 17 eyes. Fourteen eyes had narrow-angle glaucoma in the iris-block phase. The condition was acute in five eyes and chronic in nine eyes. The acute phase had persisted over 48 hours in all five eyes with acute glaucoma, a situation where iridencleisis would ordinarily have been done. In the other eyes the diagnosis of chronic iris-block glaucoma was supported by a constantly elevated tension, gonioscopically closed angles, and other clinical evidence.

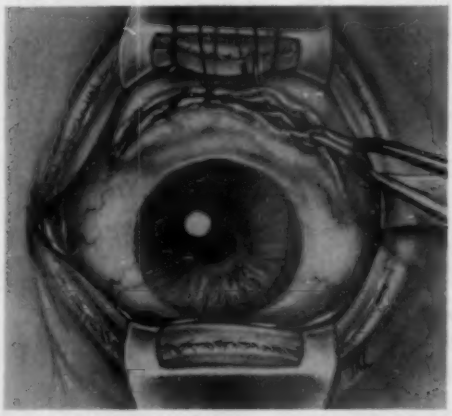

Fig. 10 (Scheie). Suturing cut edges of both conjunctiva and Tenon's capsule.

The results in controlling tension have been excellent. They were particularly gratifying in the 14 eyes operated for narrow-angle glaucoma, in which group no failures occurred. The ocular tension was considered to be controlled if repeated tension recordings were under 30 mm. Hg (Schiøtz—1948 calibration scale). In the five eyes with neglected acute glaucoma, the attack had persisted for several days in three eyes and well over a week in two eyes. In the other nine eyes angle closure had developed more slowly, with no congestion in seven and congestion in two. Although the tension was controlled in all of these eyes, hypotony resulted in three. Of 27 eyes with chronic simple glaucoma, the angles were extremely narrow in 17 and nicely open or wide in 10. The tension was controlled with normal tension in 15 eyes and hypotony in six. In six eyes the tension was not reduced to normal but the level was much less than prior to surgery and could be controlled by miotics. No explanation is offered for the greater incidence of success in narrow-angle glaucoma than in chronic simple glaucoma.

The operation has several virtues. It is extremely simple to do and is no more difficult technically than peripheral iridectomy which is one of the safest of intraocular operations. Because of its simplicity and the paucity of bleeding it is an excellent procedure for neglected acute glaucoma with a congested globe. It also leaves the eye with a much more normal appearance than other fistulizing operations.

The bleb is usually thick and should be much less prone to develop late infection than the thin, polycystic bleb which follows corneoscleral trephination. The bleb usually resembles that which follows an iridencleisis except that iris is not incarcerated and the danger of sympathetic ophthalmia should be less. It is rarely markedly elevated and polycystic.

The operation can be done on any meridian of the globe and can be performed when other procedures have failed. It also can be performed inferiorly to leave the upper portion of the globe undisturbed for cataract extraction when lens changes are marked.

No operative complications were encountered in this series of eyes. Two patients developed small hyphemas during the first three or four days after operation, but they absorbed without difficulty. Late reformation of the anterior chamber occasionally caused concern but this situation can be anticipated following any fistulizing procedure. In no instance did it interfere with the outcome. Hypotony occurred in nine eyes. This incidence seemed higher than following iridencleisis, and it is probably comparable to that of corneoscleral trephination. Hypotony was defined as a tension of 10 mm. Hg (Schiøtz) or lower. The hypotony in no instance caused dimunition of vision or other visual difficulty.

No estimate can be made of late complications, since the patients have been followed for no longer than 14 months. Late cataractous changes probably will occur as they do following any fistulizing procedure for glaucoma. The operation, however, usually avoids the insertion of an instrument into the anterior chamber and thus avoids injury to the lens at the time of operation.

The procedure was employed for a few eyes with miscellaneous types of glaucoma. It failed in two patients with hemorrhagic glaucoma but did control the pressure in one eye with glaucoma secondary to heterochromic iridocyclitis. Three eyes with infantile glaucoma were also operated but they had been badly mutilated by previous operation of various types. The tension was controlled in one.

Summary

A new filtering operation for glaucoma is described. Filtration is accomplished by causing the lips of a scleral incision, made as for peripheral iridectomy, to gape by superficial application of a galvanocautery. Upon completion of the cauterization, a peripheral iridectomy is done. The operation is as simple as peripheral iridectomy and is accompanied by few complications. The eye retains a remarkably normal appearance.

The procedure has been quite effective in controlling ocular tension. It controlled the pressure in 21 of 27 eyes with chronic simple glaucoma and 14 eyes operated for narrow-angle (iris-block) glaucoma. Hypotony resulted in nine eyes of the entire group.

The operation cannot be evaluated finally until more time has elapsed and other surgeons have an opportunity to report their own results but the observations reported in this paper indicate that the operation can be employed whenever a filtering operation is indicated. It seems at least it will be a worth while addition to our surgical resources against glaucoma. It may be of greatest value in the management of neglected, acute congestive (narrow-angle, iris-block) glaucoma where iridencleisis previously has been considered the operation of choice. Peripheral iridectomy with cautery is much easier to perform on these congested eyes, and it is accompanied by considerably less danger of hemorrhage.

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LEVATOR ADVANCEMENT AND RESECTION WITHOUT TARSECTOMY FOR BLEPHAROPTOSIS*

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Sir Stewart Duke-Elder[1] has pointed out that the treatment of congenital ptosis is essentially surgical but that the "results are not always good." With this classic application of British understatement, our distinguished colleague has concisely presented the contemporary status of surgery for blepharoptosis. Success is achieved in many cases but the uncertainty of results and the complexity of available surgical techniques have discouraged many ophthalmologists from undertaking treatment of this relatively common group of anomalies. It is our purpose tc describe a relatively simple technique of levator advancement without tarsectomy. The amount of advancement which can be obtained by this technique generally is adequate so that only that part of the levator distal to the orbital septum needs be resected. Dissection into the orbit, therefore, is obviated. Easily recognized anatomic land marks are used as guides for dissection and placement of sutures. This technique has been developed in the Children's Eye Clinic at the University of Oregon Medical School in recent years and has been used in more than 50 patients with ptosis, mainly of the congenital type.

Our operation, like all levator resections, fundamentally is a modification of the procedures described by DeBlaskovics;[2, 3] therefore, it is essential to review briefly the principles outlined by him. DeBlaskovics resected both the upper part of the tarsal plate and a variable amount of the levator muscle. He then attached the shortened levator to the new upper edge of the tarsal plate. In effect, he advanced the levator only by shortening the tarsus and most of the correction was obtained by the resection. Then he made a lid fold, either by a separate row of sutures or by passing the suture from the upper tarsus out through the skin at the site selected for the lid fold. These sutures were tied on the skin side over a plastic or rubber peg.

In using the original DeBlaskovics technique, the surgeon must solve problems of surgical judgement in each patient before satisfactory functional and cosmetic results can be obtained. In each case an exacting amount of tarsal plate must be resected. Also, a proper amount of levator must be excised without significantly disturbing the anatomic attachments of the upper lid or the orbital septum, but this amount is not possible to estimate accurately. In 1923, DeBlaskovics[3] stated: "In this operation the exact amount of tissue removal is difficult to ascertain. It is impossible to formulate any rule expressed mathematically as the lid shows a different resistance power in each case."

The difficulty of evaluating how much lev-

* From the Department of Ophthalmology at the University of Oregon Medical School. Movie made possible by a grant from the Oregon State Elks Association.

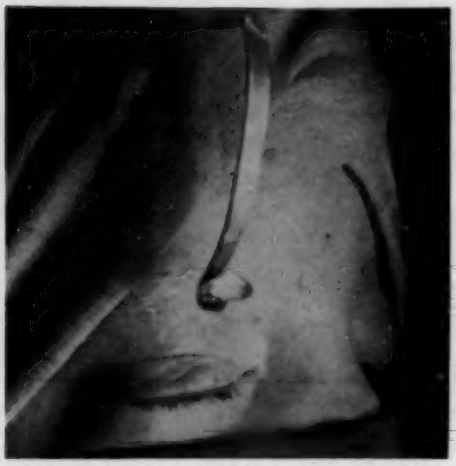

Fig. 1 (Swan and Keizer). Simple self-retaining lid everter designed by John P. Keizer.

ator to resect has bothered other surgeons. In 1952, Berke[4] wrote that: "In every case an estimate was made of the amount of levator tissue excised. These measurements were compared to the amount of correction achieved. No correlation could be detected. The only rule which we have found satisfactory in this respect is: excise enough levator tissue at the time of the operation to raise the upper lid to or above the limbus."

Fig. 3 (Swan and Keizer). A conjunctival incision is made about two mm. above the upper border of the tarsus where the conjunctiva is easily separated from Müller's muscle. A rim of conjunctiva is left at the upper border of the tarsus to permit sutures to be placed at the end of the operation.

Fig. 2 (Swan and Keizer). Double eversion of the lid by the Keizer retractor exposes the upper edge of the tarsus and the superior fornix. A self-adjusting drape covers all of the face except the operative area.

Fig. 4 (Swan and Keizer). The conjunctiva is dissected from Müller's muscle almost to the superior fornix and is reflected as a single flap. On the temporal side care is taken to avoid injury to the lacrimal gland and its ducts. Bleeding is controlled by suction through a plastic tube.

Fig. 5 (Swan and Keizer). Müller's muscle is grasped on the lateral edge with forceps. A buttonhole is made with scissors so that the muscle attachment to the upper edge of the tarsus can be severed.

Fig. 7 (Swan and Keizer). Five equidistance O'Brien lock stitches[8] are placed in the levator just in front of the orbital septum. Absorbable sutures are used. Care is taken to avoid incorporation of the orbital septum; otherwise, the eyelid will not close properly or follow the eye in downward gaze.

To satisfy this rule, many authors have advocated dissection of the levator well back into the orbit even sectioning the aponeurosis at its lateral attachments. It occurred to us that this extensive dissection could be avoided if the levator could be advanced farther than just to the upper edge of the shortened tarsus; that is, to the lid margin. Could this be achieved by resecting more of the tarsus than was advocated by DeBlaskovics? We didn't believe that this would be desira-

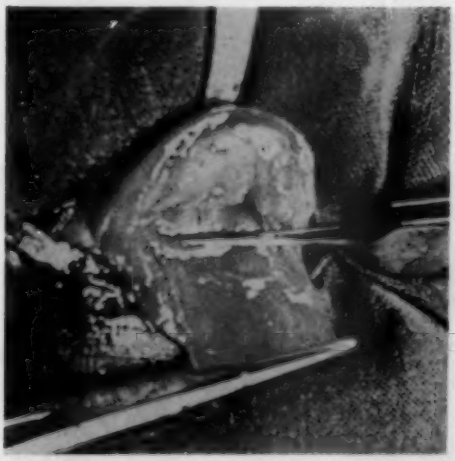

Fig. 6 (Swan and Keizer). Müller's muscle and the levator are clamped and reflected. The forceps blades mark the line of penetration of the orbital septum by the levator.

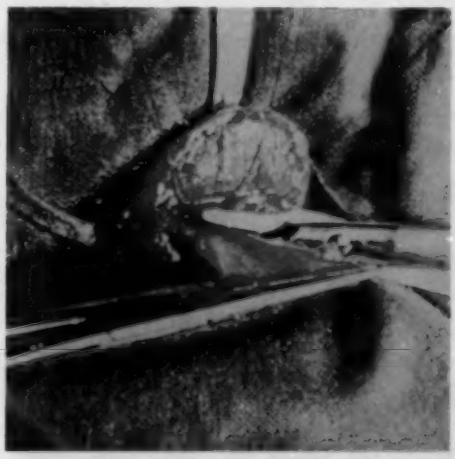

Fig. 8 (Swan and Keizer). The orbital septum has been separated from its attachment to the levator so that it will not be pulled forward with the advancement of the muscle. The levator distal to the sutures then is excised.

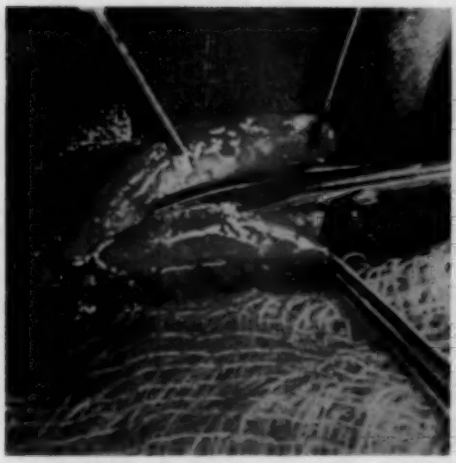

Fig. 9 (Swan and Keizer). The lid everter has been removed. The upper edge of the tarsus has been grasped with forceps and the front surface of the tarsus is being separated from the orbicularis. The roll of orbicularis fibers can be seen between the scissor blades and the sutures.

Fig. 11 (Swan and Keizer). The knots have been tied. The edge of the resected levator now is attached to the lid margin between the orbicularis fibers and the tarsus; thereby, a wide, true advancement has been made.

ble or that tarsectomy was even essential.

Tarsectomy has been advocated in ptosis surgery for two reasons, to shorten the distance between the levator attachment and the lid margin and to avoid buckling of the tarsus by the elevated lid. We wanted to avoid removing any of the tarsus because it is the skeleton of the lid and is essential to a proper fitting of the eyelid to the globe. Instead, we have left the tarsus intact and have advanced the edge of the resected levator muscle in front of the tarsal plate to attach it by ab-

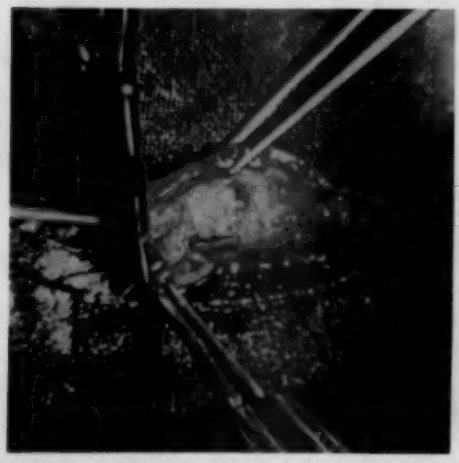

Fig. 10 (Swan and Keizer). The tough tissue at the lid margin is identified by the black bulbs of the eyelashes. The sutures are passed into this tissue by wide, deep bites.

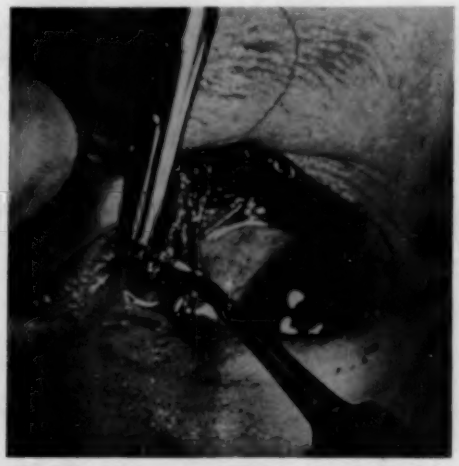

Fig. 12 (Swan and Keizer). The conjunctival incision is closed with multiple, fine absorbable sutures. The knots are above the tarsus and, therefore, cause little or no irritation of the cornea.

sorbable sutures to the tough tissue at the lower and anterior edge of the tarsus. This tissue contains the follicles of the lash line. Advancement of the levator to this point helps to evert the eyelashes. In the placement of these sutures, two errors must be avoided. If the sutures are not passed deeply into the tough tissue, they will pull out and the operative result will be poor. On the other hand, if the sutures are passed into the tarsus alone, the tarsal part of the lid margin will be satisfactorily elevated but there will be a redundancy of skin at the lid margin and the eyelashes will be turned down. Stated otherwise, the sutures must be so placed in the tough tissue at the base of the tarsus that both the outer cutaneous and orbicularis section of the lid and inner tarsal and conjunctival section are elevated to the same degree.

In effect, our procedure permits an advancement of the levator equivalent to the full width of the tarsal plate and obviates dissection of the levator beyond the orbital septum. In every operative case, it has been possible to bring the lid margin just above the limbus when the patient was still under moderately deep general anesthesia. Also, we have found that it is unnecessary to resect any part of the tarsus to avoid buckling. It has been our experience that the tarsus will buckle horizontally only if the levator is attached to its anterior surface in the middle of a plate above the lid margin. Buckling does not occur if the levator is advanced to the lower edge of the plate and if the upper edge of the tarsus is resutured to the conjunctiva.

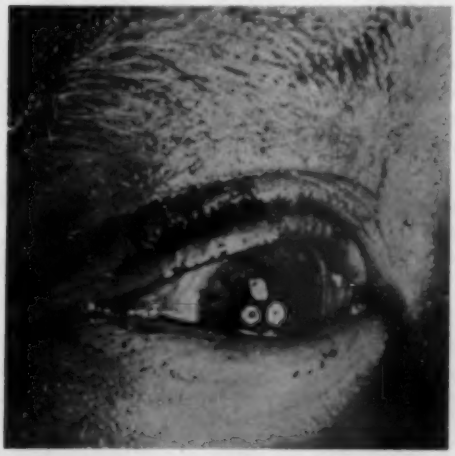

Fig. 13 (Swan and Keizer). At the end of the operation with the child under moderately deep anesthesia, the lid margin should be at the upper limbus and the eyelashes should be everted. At this point, the surgeon should pull down the lid with forceps to be certain that it closes readily. Resistance to closure means that the orbital septum has been incorporated in the sutures.

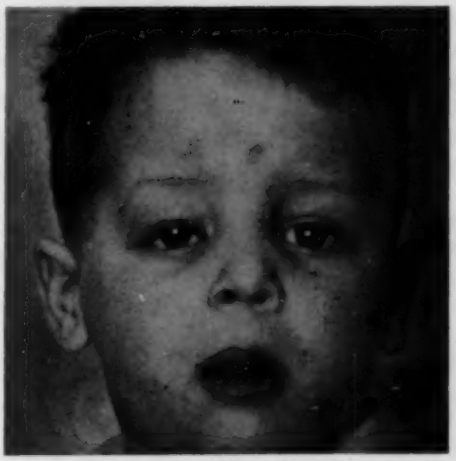

Fig. 14 (Swan and Keizer). Appearance of the operated right lid one month after surgery for marked congenital ptosis. A lid fold has developed in this child without additional sutures.

In the past, extensive advancements such as we have recommended have been avoided because it was feared that the lid would not close properly. We have demonstrated to our satisfaction that when restriction of lid closure occurs, it generally is due to the incorporation of the edge of the orbital septum along with the levator in the advancement sutures. If this is done the lid is suspended by this inelastic fascial structure from the upper edge of the orbital rim. In our procedure, a conjunctival incision is made above the tarsus. The conjunctiva is reflected posteriorly. Then, the levator is dissected back

only to the orbital septum. Great care is taken not to incorporate this structure in the placement of the advancement sutures. Furthermore, we free it from the levator so that it will not be pulled forward with the advanced levator.

In many cases, a good lid fold will form with the mere advancement of the levator to the lid margin. In others it is obtained by placing a row of five or six interrupted sutures which enter the skin at the desired area for the lid fold and pass through the full thickness of the lid into the superior fornix.

No temporary sutures are necessary to suspend or immobilize the lid during the healing period. A condensation cone of cleared X-ray film generally is used without any other dressings. This can be discontinued within a few days.

The details of our technique are presented in the illustrations herein reproduced. These have been taken from a movie presented at the 1957 meeting of the Pacific Coast Oto-Ophthalmological Society. In this case the surgery was performed by a member of the resident staff, Homer R. Crisman. Photography was by another member of the resident staff, Paul Bailey, Jr. It has been our experience that the technique can be mastered by resident surgeons early in their training.

Summary

A simple and effective technique of levator resection and true advancement is described and illustrated. Neither orbital dissection nor tarsectomy is required. Easily identified landmarks simplify dissection and placement of sutures.

The conjunctiva is incised just above the tarsus and is reflected toward the superior fornix. Müller's muscle is detached from the tarsus and along with the levator is resected almost to the orbital septum. No dissection is made into the orbit and the aponeurosis is not disturbed; however, the orbital septum is separated from the levator so that it will not be pulled forward with the advancement. The resected levator is advanced the full width of the tarsus and is attached by absorbable sutures to the tough tissue surrounding the eyelash follicles at the lid margin. This elevates evenly both the tarsal and the musculo-cutaneous sections of the eyelid. Care is taken to avoid incorporation of the inelastic orbital septum in the sutures; otherwise, the lid will not close well. The knots are buried deep to the orbicularis, but are in front of the tarsus. Resection of the tarsus is unnecessary but the conjunctiva always is sutured with fine absorbable sutures. In some cases an extra row of sutures may be necessary to create a lid fold.

Postoperative care is simple because there are no sutures to remove and the lids generally close well. No traction sutures are required to elevate the lid during the healing period. The only dressing used is a transparent shield. The operation has been used in nearly 50 patients at the University of Oregon Medical School and can be performed effectively by resident surgeons.

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HYPERPLASIA OF THE RETINAL PIGMENT EPITHELIUM*

Simulating a neoplasm: report of two cases

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Introduction

The pigment epithelium of the retina is an extremely interesting and versatile tissue, which proliferates on the slightest provocation. The newly formed tissue may have the characteristics of the parent pigmented epithelial cell or, through metaplasia, become an entirely different cell type ranging from bladder cells to connective tissue.

It is unusual to see retinal pigment epithelium extending into the optic disc. We have on record two such cases in which the vision was disturbed to such an extent that malignancies were suspected and the eyes were enucleated.

Case reports

Case 1

A girl aged 11 years, during a routine examination at the soldiers' home, was found to have in the left eye a grayish-brown lesion involving the lower temporal quadrant of the disc and adjacent retina. There was no complaint of visual loss; her visual acuity was 20/20. She came to the Illinois Eye and Ear Infirmary and was found to have a small enlargement of the blind spot extending upward in the anticipated region from the involved retina.

The patient was followed by Dr. Floyd at intervals of about a month, and it was the opinion of him and consultants who were seeing her that there was some enlargement of the lesion and also some increase in its thickness. There was also rather definite increased striation of the retina. Perhaps the most striking change of all was the gradual and consistent increase in the area of the scotoma. In three months' time the lesion was seen to be larger, more nodular, and appeared to be elevated about two diopters; retinal striae increased. For these reasons it was thought the lesion might be neoplastic—probably a melanoma—and the eye was enucleated.

Calottes showed the retina in situ, and a slightly raised pigmented lesion on, below, and temporal to the disc.

On microscopic examination the retina appeared normal except in the region of the disc, where there was abnormal thickening of the retina extending about one disc diameter beyond the lower temporal edge of the thickened disc. Throughout this thickened lesion there was an irregular distribution of pigment which originated from an infolding of retinal pigment epithelium.

Adjacent to the optic nerve the pigment epithelium made a sharp turn and proliferated into the retinal stroma, arranging itself in single file about capillaries and spaces. Hyaline tissue resembling Bruch's membrane surrounded some of the pigment cells. The lesion contained many fine capillaries and small glial cells in a fibrillar stroma arranged about the inferior temporal artery. Adjacent to the optic nerve, beneath this hyperplastic mass, the nuclear layers were pushed away from the optic foramen.

Our first diagnosis was benign epithelioma of the retinal pigment epithelium. Comparing the proliferation of the pigment epithelium of this case (7076) with the second case being reported (P1333) it is thought best to place both diagnoses as noted in the title of this paper—hyperplasia of the retinal pigment epithelium.

Case 2

A boy, at the age of 11 years, was advised by the school nurse to see an eye doctor because of defective vision in his right eye. The doctor "found a tumor of the optic disc, and treated it with shots," and reported that the vision of this eye was 20/50 before and after the treatment was discontinued.

This patient was seen by one of us (Theobald) the following year, when his vision was 20/70 in the right eye. Vision in the left eye always was and is 20/20.

The right disc looked like a white doughnut, elevated, but not edematous. Striae, like opaque nerve fibers, radiated in all directions, but mostly up and down. The vision with this eye was 20/40 when he first entered school but it gradually decreased until the eye was enucleated.

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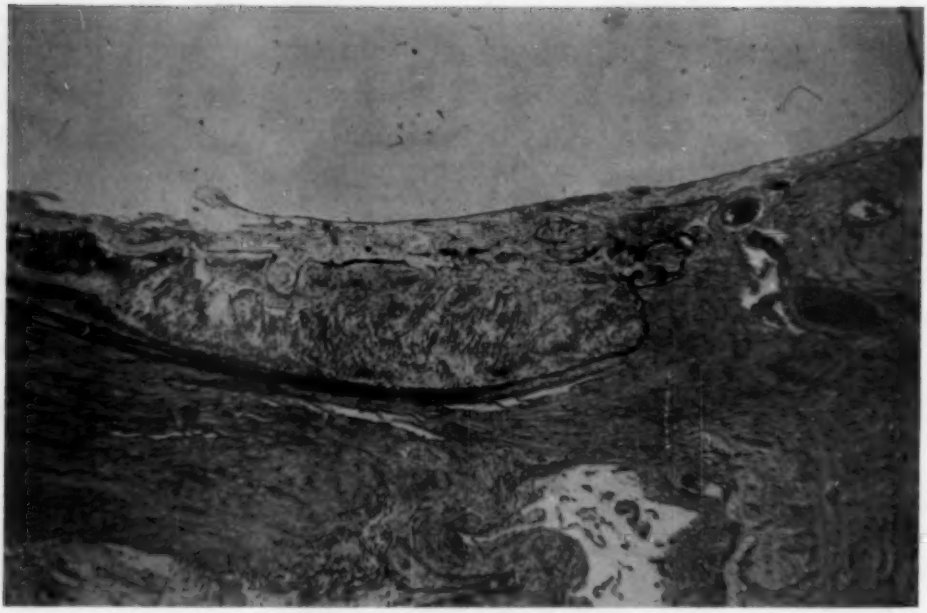

FIG. 1 (Theobald, Floyd, and Kirk). *Case 1.* This section shows proliferation of pigment epithelium into the overlying retina.

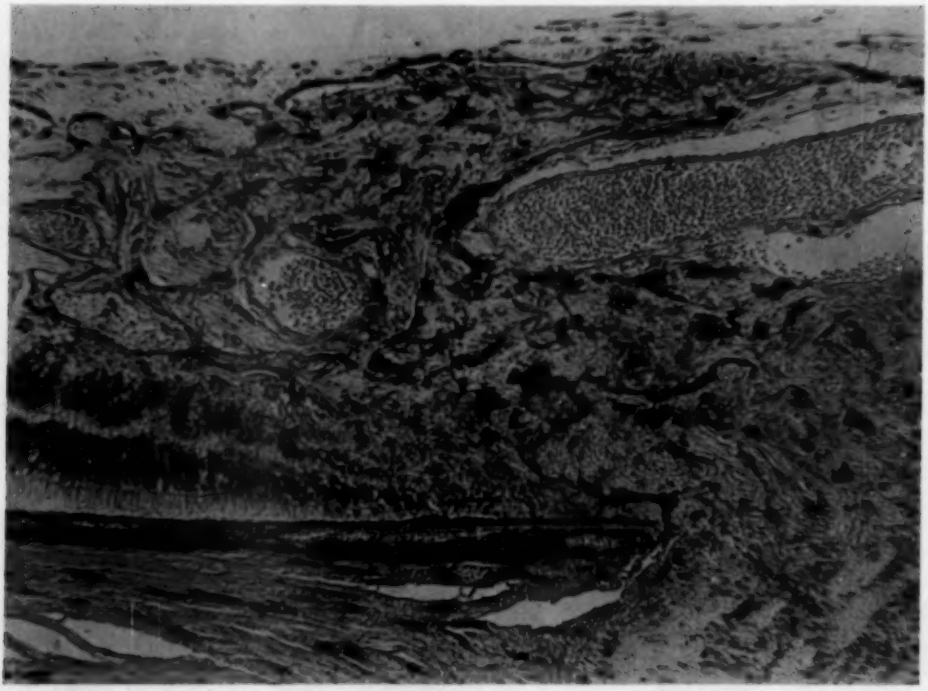

Fig. 2 (Theobald, Floyd, and Kirk). *Case 1.* This shows the spiral-like proliferations of pigment epithelium winding and bending into the retina and optic nerve.

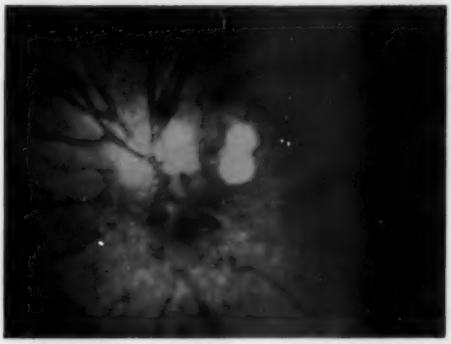

Fig. 3 (Theobald, Floyd, and Kirk). *Case 1.* This fundus picture was taken when the patient was first seen on April 23, 1949. The field made at the same time is shown in Figure 5-A.

A year later at the age of 13 years, the boy was seen by a neurologist who found the vision reduced to 20/200 and the same fundus picture as already described. He made the diagnosis of glioma of the optic nerve and enucleated the eye by the transcranial route. The eye was given to Dr. Theobald for section. The remaining optic nerve was pathologically negative.

On gross examination, lateral calottes showed the retina in situ. The optic disc was doughnut shaped, raised, and three mm. in diameter.

Microscopic examination showed the disc to be edematous and thickened by proliferated glial cells. In the disc were many cavities of various sizes, filled with hyalinized transudate of varying density —some even calcareous. These cavities were surrounded by masses of tissues composed of strands of proliferated pigment epithelium which were separated by homogenous hyalinized material.

Fig. 4 (Theobald, Floyd, and Kirk). *Case 1.* The fundus picture taken just before enucleation, showing enlargement of the pigmented area. The field made at the same time, March 15, 1950, may be seen in Figure 5-B.

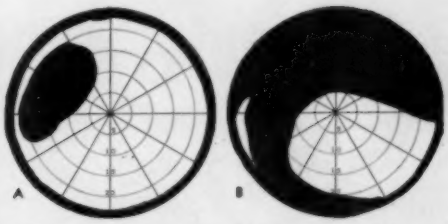

Fig. 5 (Theobald, Floyd, and Kirk). *Case 1.* (A) Field of the left eye made on April 23, 1949. Vision: 20/20. Two-mm. white target. (B) Field of left eye made on March 15, 1950. Vision: 20/20. two-mm. white target.

Discussion

This homogenous noncellular tissue was, in all probability, laid down by the proliferated pigment cells. It is most likely that the proliferation of the pigment cells slowly impeded circulation within the optic disc and caused the development of the serum-filled cavities. This, in turn, caused the glial-cell proliferation and gradual loss of vision. Such hyalinized formations are called drusen, or hyalin bodies. The word drusen means "warts" and is usually applied to excrecences of Descemet's and Bruch's membranes.

Theories as to the origin of the hyalin (Duke-Elder) are:

1. Parsons (1905): Originates from exudates laid down in the nerve head, possibly from a previous inflammatory process which may have left no evidence of its existence.
2. Müller (1858): Outgrowths of Bruch's membrane, derived from the pigment epithelium, displaced into the disc.
3. A. Fuchs (1927): Neural origin, on account of close association with neuroglia.
4. Duke-Elder: "All that can be said is that they seem to represent the deposition of a hyalin-like material because of some local metabolic disturbance of unknown and probably varied etiology."

Summary

Two cases of proliferation of the retinal pigment epithelium are reported; each presented a different clinical picture.

Fig. 6 (Theobald, Floyd, and Kirk). *Case 2.* Glial proliferation on disc, multiple drusen or hyalin bodies, and massive proliferation of pigment epithelium into disc.

Fig. 7 (Theobald, Floyd, and Kirk). *Case 2.* This section was made at a different level. It shows massive proliferation into the optic nerve.

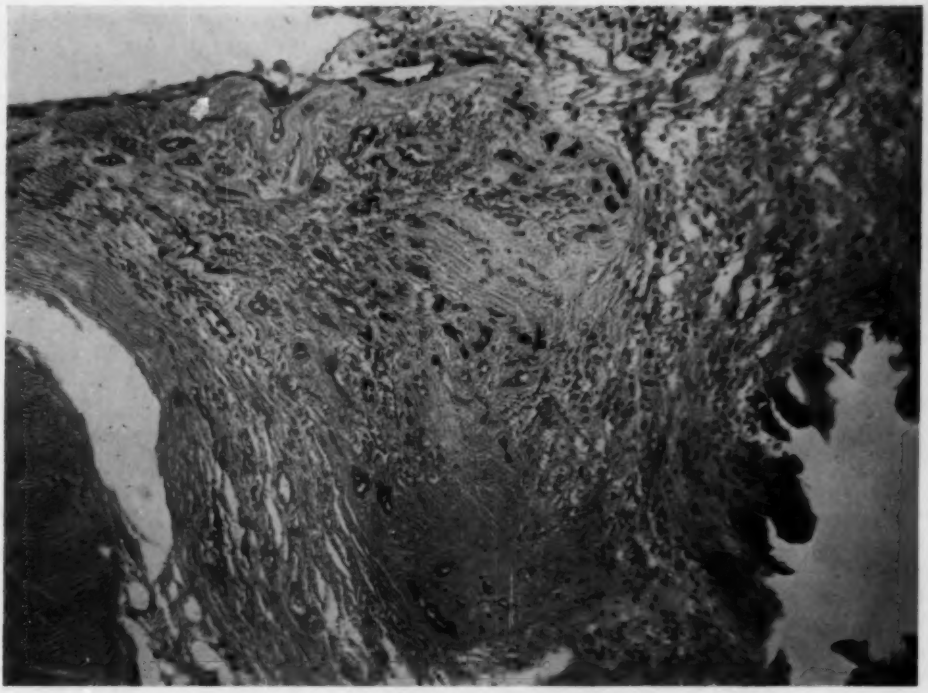

Fig. 8 (Theobald, Floyd, and Kirk). *Case 2.* This section, made at a different level, shows massive proliferation into the optic nerve.

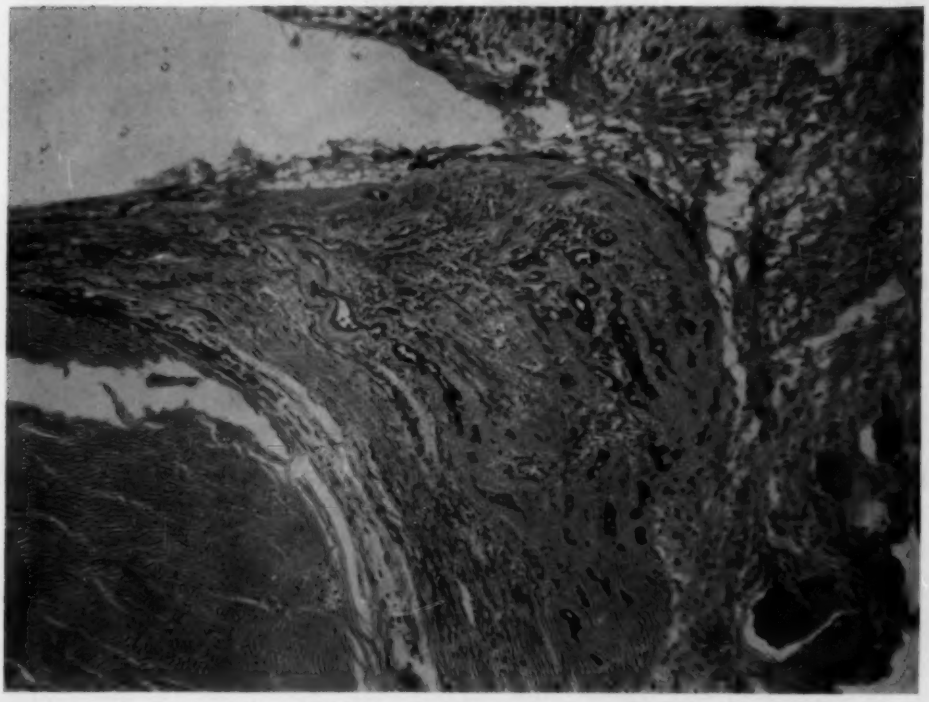

Fig. 9 (Theobald, Floyd, and Kirk). *Case 2.* Another section, made at a different level, shows massive proliferation into the optic nerve.

Case 1, that of an 11-year-old girl, showed a pigmented lesion due to proliferation of the pigment epithelium into the retinal stroma.

Case 2, that of a 13-year-old boy, showed a tumefaction of the optic disc due to a proliferation of the pigment epithelium into the optic nerve associated with multiple drusen or hyalin bodies.

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CYTOLOGIC OBSERVATIONS ON HERPETIC KERATITIS*

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Herpetic keratitis is now generally recognized as one of the most common types of keratitis in the United States, and as the most important type so far as economic and visual loss are concerned. The typical manifestation, dendritic keratitis, can be diagnosed clinically without difficulty in its early stage, but recurrent or atypical cases may present a troublesome diagnostic problem. In early cases a definitive diagnosis can be based on the isolation of the virus in tissue culture, on the chorioallantois of the developing chick embryo, or on rabbit cornea, but these are procedures not available to every ophthalmologist.

The need is for a simple way of making a diagnosis with slide and microscope, as is possible in the differential diagnosis of bacterial and mycotic ulcers. Through the work of Tzanck[1] and Blank and associates,[2] such a method has for the past few years been available to dermatologists for the recognition of certain viral skin infections. These investigators were able to show that scrapings from the skin vesicles of herpes simplex, herpes zoster, and varicella contain characteristic giant multinucleated epithelial cells that are not to be found in the skin vesicles of other diseases. Blank and Rake[3] found similar giant cells in scrapings from experimental herpes simplex keratitis in the rabbit.

Unfortunately no means of differentiating the skin lesions of herpes zoster, varicella, and herpes simplex were discovered. However, since the corneal lesions of herpes zoster and varicella have a distinctive appearance and association with cutaneous disease, it would seem that if cell changes characteristic of the group should be found in keratitis not due to varicella or zoster, they might reasonably be regarded as a specific indication of herpes simplex.

In an effort to identify such changes, scrapings from experimental herpetic keratitis in the rabbit, and from clinical keratitis known to be or suspected of being herpetic, have been compared with scrapings from other types of keratitis. After proper corneal anesthesia, light scrapings from areas of greatest disease activity were taken with a platinum spatula, fixed with methyl alcohol, and stained with Giemsa.

The nonspecificity of the intranuclear inclusion bodies of herpes-simplex virus has nullified their value in the diagnosis of skin

* From the Department of Ophthalmology and the Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco. Supported in part by a grant from the National Institutes of Health (B-604).

lesions. Their presence on the cornea, however, would have a diagnostic significance comparable to that of the giant viral epithelial cell referred to above, and for the same reason. In spite of the fact that intranuclear inclusions, unlike cytoplasmic inclusions, have in the past been very hard to demonstrate in scrapings, a search for them was undertaken as an integral part of the present investigation. Past efforts to identify herpes elementary bodies in scrapings have also been fruitless, but this too was attempted. Slides for this purpose from cases of typical dendritic keratitis were stained with Victoria blue.

Cytology of experimental herpetic keratitis in the rabbit

Scrapings from the corneas of 10 rabbits infected with herpes simplex virus by the scratch method were taken at various stages of the disease and studied for characteristic cell changes, for the presence of intranuclear inclusions, and for free herpetic elementary bodies. The eyes of eight additional rabbits, similarly infected, were sectioned at the height of their infections.

The leukocytic reaction in all 18 rabbits was nonspecific. In every case, however, typical giant multinucleated epithelial cells like those described by Tzanck[1] and by Blank and associates[2] were found without difficulty in both scrapings and sections. They were most numerous early in the disease and disappeared with healing.

Scrapings stained with Victoria blue were scrutinized for elementary bodies. Although free bodies of elementary-body size were seen, their numbers in any one case were diagnostically insignificant.

In scrapings it was impossible to identify intranuclear inclusions, even in giant cells, with any certainty; faint, suggestive outlines were frequently seen but were never clear-cut. In corneal sections, on the other hand, inclusions were readily identifiable, especially within the nuclei of the giant cells. It seemed likely that in scrapings the nuclear envelope of marginated chromatin obscured inclusion material that could be seen unobscured in nuclear cross-sections.

A few attempts were made to demonstrate inclusions by the wet fixation method of Lindner[4] in which cells in scrapings are not allowed to dry out and flatten but retain their depth as in sections. Inclusions could be seen in some of these preparations but the technique is too cumbersome to be of practical value.

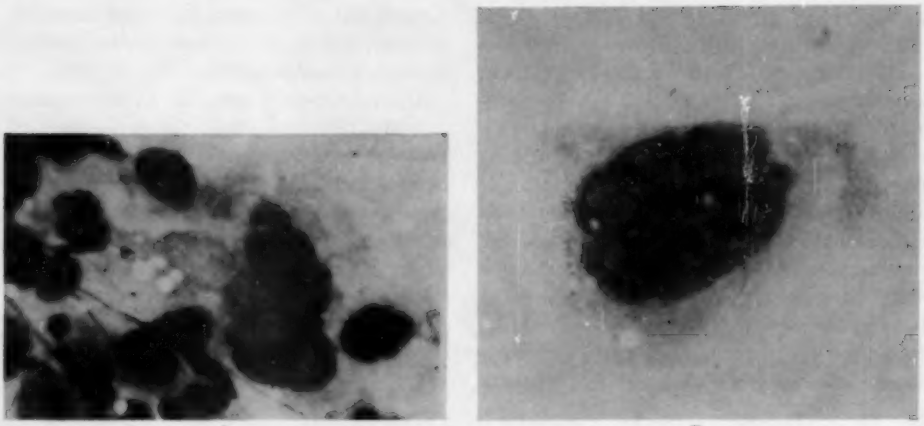
Cytology of epithelial scrapings in dendritic keratitis

Available for study were epithelial scrapings from 38 cases of dendritic keratitis from various sources, including the University Eye Clinic, my own private practice, and the practices of my colleagues. In all of these a definite diagnosis of herpes simplex virus keratitis was made on the basis of characteristic dendritic figures.

The leukocytic picture in these scrapings was entirely nonspecific. The leukocytes were few in number and largely mononuclear. Some scattered neutrophils were also seen but no eosinophils, basophils, or macrophages.

Typical multinucleated giant epithelial cells were found in 28 of the 38 cases, generally in small numbers. They varied in size from small cells containing only a few nuclei to very large cells containing a great many (fig. 1). They also varied in number from slide to slide, from a single cell on one to 26 on another. The abnormal cells could be recognized readily under low power magnification, only a few minutes being required for the rapid scanning of a slide. In two cases from which the first preparations were negative, slides prepared later were positive. It seemed more than likely that giant cells would be found in every case with typical active dendritic figures if the sampling were done with sufficient care and repeated when necessary.

Scrapings from 10 cases were stained with Victoria blue and searched for elementary



A B

Fig. 1 (Thygeson). (A) Giant multinucleated epithelial cell in scraping from dendritic keratitis. (Giemsa, ×1000.) (B) Giant multinucleated epithelial cell from dendritic keratitis. Vague outlines of inclusion bodies can be seen within the nuclei. (Giemsa, ×1000.)

bodies. As in experimental herpetic keratitis, a few granules believed to be elementary bodies were seen but they were not present in clumps or in sufficient numbers to be diagnostic. These results paralleled those obtained by me in extensive unreported studies in which various elementary body stains have been employed.

All attempts to make unequivocal identification of herpetic intranuclear inclusion bodies in scrapings were unsuccessful.

Cytology of epithelial scrapings in herpetic disciform keratitis

Scrapings were taken from 18 cases of disciform keratitis known to have followed dendritic keratitis and therefore to be herpetic in origin. Epithelium was obtainable in most instances but ulceration had supervened in two and from these only stromal material appeared on the slides.

Here again no characteristic leukocytic formula could be demonstrated. A paucity of

TABLE 1

Cytologic changes observed in herpetic and nonherpetic keratitis

	Total Cases	Cases with Giant Multinucleated Epithelial Cells	Cases with Inclusions	Cases with Elementary Bodies
Experimental herpetic keratitis in rabbit	18	18	?	?
Dendritic keratitis	38	28	?	?
Herpetic disciform keratitis	18	4	?	—
Superficial keratitis (suspected of being herpetic)	32	9	?	—
Nonherpetic superficial keratitis:				
Trachoma	6	0	6	6
Phlyctenulosis	2	0	—	—
Acne rosacea keratitis	3	0	—	—
Keratitis sicca	4	0	—	—
Relapsing keratitis	3	0	—	—
Superficial punctate keratitis	2	0	—	—
Catarrhal ulcer	22	0	—	—
Central ulcer, bacterial or mycotic	11	0	—	—

leukocytes, mononuclear and neutrophilic, were seen but no eosinophils or basophils. Giant multinucleated epithelial cells were demonstrated in only four of the 18 cases. No intranuclear inclusions were found. A search for elementary bodies in this group was not attempted.

Cytology of epithelial scrapings in atypical superficial keratitis suspected of being herpetic

Scrapings were available for study from 32 cases without typical dendritic keratitis but in which herpes was suspected because of negative bacterial and mycotic findings in combination with chronicity, corneal anesthesia, or morphologic findings suggestive of herpes, as for example, the so-called "geographic ulcer." Among these were four cases of chronic epithelial keratitis without ulceration in which the epithelial opacification was localized in one or more ameboid plaques.

Again no characteristic leukocytic pattern could be demonstrated in any case, nor could inclusion bodies be identified with certainty although vague outlines which may have represented inclusions were seen in certain cells. No search for elementary bodies was attempted.

Typical giant multinucleated epithelial cells were found in only nine of the 32 cases but it is of interest that they appeared in three of the four cases of bizarre epithelial keratitis described above.

Cytology of miscellaneous forms of nonherpetic superficial keratitis

Epithelial scrapings were taken from a number of forms of superficial keratitis from which herpes could be definitely excluded. Among these were six cases of trachoma, two of phlyctenulosis with corneal phlyctenules, three of acne rosacea keratitis, four of keratitis sicca, three of relapsing keratitis (recurrent erosion after trauma), two of superficial punctate keratitis, 22 of catarrhal ulcer, and 11 of central ulcers known to be bacterial or mycotic.

In scrapings from trachoma, taken in each instance from the peripheral cornea just within the upper limbus (the site of maximal trachomatous activity), a few epithelial cells with two to four nuclei were seen, comparable to those found in conjunctival scrapings from trachoma. They did not resemble the giant multinucleated epithelial cells of herpes simplex. A few cells similar to those seen in trachoma were also found in scrapings from the two cases of superficial punctate keratitis. In the remaining scrapings no multinucleated epithelial cells of any kind could be demonstrated. Particular attention was given to scrapings from catarrhal ulcers because of their occasional confusion with early atypical dendritic ulcer.

Since topical steroids, contraindicated for dendritic keratitis, are the treatment of choice for catarrhal marginal ulcers, a microscopic aid to differential diagnosis at an early stage would be helpful. It is noteworthy, therefore, that giant cells were consistently absent from material taken from the 22 cases of catarrhal ulcer; on the basis of follow-up clinical studies on all of these, herpes simplex virus was excluded as a possible cause.

Characteristics of the giant multinucleated epithelial cell

The morphologic characteristics of this virus-type multinucleated giant epithelial cell as found in the skin in herpes simplex, herpes zoster, and varicella have been well described by Blank and associates.[2] The same cell was found on the rabbit cornea in experimental herpes simplex keratitis by Blank and Rake[3] and is well described in their textbook, *Viral and Rickettsial Diseases of the Skin, Eye, and Mucous Membranes of Man.* Unlike the giant cells from the skin, those from the cornea do not contain melanin granules. Otherwise the morphologic pictures seem to be identical. A typical cell contains up to 15 nuclei. The normal nucleoli are generally absent, and the normal chromatin pattern of each nucleus has been altered to a stringy, amorphous pattern. The cyto-

plasm is scant and stains a light blue with Giemsa. The cells are often enormous, with diameters four or five times those of normal corneal epithelial cells.

Discussion

The results of this study seem to indicate that intranuclear inclusion bodies cannot be demonstrated in corneal scrapings from herpetic keratitis with sufficient regularity to be of diagnostic value. This was the case even in the experimental disease of the rabbit, during both the incubation period and at the height of the clinical disease. The relative ease with which such inclusions can be demonstrated in sections of cornea from experimental herpetic keratitis suggests that marginated chromatin enveloping the intact nucleus may obscure in scrapings inclusions which would be apparent in cross-section. Attempts to avoid this chromatin-effect by the use of other fixatives and staining methods have met with only partial success. Wet fixation as employed by Lindner[4] in the study of trachoma inclusions yielded a higher percentage of positive findings but is a cumbersome procedure not applicable to office practice.

The virus of herpes simplex is known from filtration studies and electron microscope photographs to be of large particle size (175 mμ according to Coriell and associates,[5] and to be within the limits of resolution of the ordinary light microscope. With the electron microscope the virus elementary bodies have been seen lying within the nucleus, and sometimes within the cytoplasm, of affected cells. They do not stain with Giemsa or other histologic dyes, however, and so do not appear in ordinary cell preparations. Free herpes elementary bodies take special elementary body stains, such as Victoria blue. In this study, however, they could not be demonstrated in specially stained preparations with sufficient regularity or in sufficient numbers to be diagnostic.

It is clear from previous cytologic studies (Kimura and Thygeson[6]) that conjunctivitis caused by typical viruses, such as the adenoviruses and the virus of Newcastle disease, is characterized by scanty exudate and a predominance of mononuclear cells. This scanty mononuclear cell exudate has been a regular feature of the conjunctivitis in primary herpetic keratoconjunctivitis that is seen principally in young children as the initial infection with herpes simplex virus. With this in mind, a search was made for features of diagnostic value in the leukocytic pattern of corneal scrapings from herpes keratitis.

As already reported, an insignificant number of leukocytes, most of them lymphocytes, were found in typical dendritic keratitis. More leukocytes were seen in herpetic keratitis of long standing or with deep corneal involvement. They were generally mononuclear except in some cases with deep necrosis in which there were also an appreciable number of neutrophils. As would be expected, neutrophils predominated in cases complicated by secondary bacterial or mycotic infection. It may be said, in fact, that abundant neutrophils are an almost certain indication of secondary infection. This can have practical value in determining whether or not a secondary infection should be suspected, before the results of culture can be obtained.

The most important cytologic feature uncovered in this study was the regular occurrence of multinucleated giant epithelial cells in experimental herpetic keratitis and typical dendritic keratitis. To a lesser extent they were found in disciform keratitis known to be herpetic, and in keratitis suspected of being herpetic. They were not found at all in keratitis clearly nonherpetic.

The relative scarcity of giant multinucleated epithelial cells in cases of disciform keratitis corresponds with the general inability of most observers to isolate herpes virus from such cases, even when a definite dendritic figure has preceded the stromal involvement. This absence of giant cells sug-

gests that the virus may have become inactive in the epithelium while still active in the stroma.

Since similar giant cells are found in the skin vesicles of herpes zoster and varicella, their presence in zoster and varicella keratitis would be expected. Unfortunately this probability could not be tested in this study since there were no cases of varicella with keratitis, and it was impossible to obtain corneal scrapings from the only two cases of herpes zoster; in the skin vesicles of the latter, however, characteristic giant cells were readily demonstrable. In view of the ease with which varicella and zoster can be eliminated in the differential diagnosis of keratitis, the demonstration of multinucleated epithelial cells in corneal scrapings certainly warrants a presumptive diagnosis of herpes-simplex keratitis.

A simultaneous search was made for multinucleated epithelial cells in conjunctivitis. It was not uncommon to see cells with two or three nuclei in conjunctivitis due to the adenoviruses or to the viruses of trachoma or inclusion conjunctivitis. No cases of primary herpetic keratoconjunctivitis were available for study. It will be interesting to determine whether or not typical giant epithelial cells can be found in conjunctival material from this disease.

Summary and Conclusions

1. Epithelial scrapings from rabbits experimentally infected with herpetic keratitis, and from cases of human dendritic keratitis, contained giant multinucleated epithelial cells comparable to those found in scrapings from herpes-simplex vesicles of the skin. No such cells were found in scrapings from cases of nonherpetic keratitis of various types.

2. The results of attempts to demonstrate herpetic intranuclear inclusions and free herpetic elementary bodies in corneal scrapings were inconclusive.

3. The observed leukocytic reaction in herpetic keratitis was meager and without diagnostic significance although a predominance of neutrophilic leukocytes could be said to suggest secondary bacterial or mycotic infection.

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Medical Center (22).

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A CASE OF LIGNEOUS CONJUNCTIVITIS NOW 36 YEARS IN DURATION

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Distinguishing characteristics of ligneous conjunctivitis would seem to be the initial membranous conjunctivitis and the later conversion of at least one membrane into a granuloma of hyaline connective tissue. Membranes upon the conjunctiva are produced by many different causes,[7] but so far as I know only the membranes of ligneous conjunctivitis can become thus organized. Because of the woodlike firmness of the resulting granuloma, the term ligneous conjunctivitis was devised for this disease by Borel[5] in 1933, and later accepted by Paufique and Moreau[6] and others. Another term for it frequently used has been "chronic membranous conjunctivitis," but neither of these is correctly descriptive of the disease. In the beginning, it is true, the disease is membranous, but it is then acute, not chronic, and when it becomes "ligneous" and chronic it is no longer membranous or really any kind of conjunctivitis. For the disease in its chronic stage the term recurrent postmembranous granuloma of the palpebral conjunctiva would seem suitably descriptive. However, since the term ligneous conjunctivitis is distinctive and has been in use for 25 years, it seems to me it should be preferred as a designation for the whole disease until a significantly better term is brought forward. I am reporting the following case because it reveals about this disease three important facts previously unrecorded.

CASE REPORT

Ruth E., born in Nova Scotia in 1921, was first seen by me on July 24, 1937, in consultation with Dr. D. G. Cogan. She had learned from her family that at the age of about one year she had developed a large growth in the inner surface of each upper lid. She had no information as to whether or not this had resulted from an acute inflammatory condition. For the past eight years these growths had been excised about once a year by some doctor, not always the same one. They always soon returned and after reaching a large size remained about the same in appearance. They caused little if any discomfort and seldom if ever produced redness of the eyes or any discharge. Elsewhere on her body, accidental cuts had always healed quickly without leaving protruding scars.

The patient stated that three months before I first saw her, the growths had been removed by a local ophthalmologist, now deceased, who was said to have applied to them silver nitrate which impaired her vision. On examination (1937) I found that the growth had returned on the right but not on the left lid. On the right upper lid it appeared as a horizontal ovoid mass attached to the middle of the tarsus by a constricted base. It measured about 12 mm. horizontally and five mm. vertically. It was flattened, evidently by pressure of the lids, so that its greatest thickness was only about four mm. At its margins it became thin and pale for about three mm. Elsewhere it was about the color of the palpebral conjunctiva. Its constricted base was circular and only about four mm. in diameter. The left lid showed a marked scar, but no definite protuberance. (To explain this, I assume that, although the patient had not so stated, the growth on the left lid had been recently removed.) Both lower lids were entirely normal. There were no preauricular or other glandular enlargements. Both corneas showed superficial opacities and some vascularization, presumably as results of the treatment with silver nitrate. The visual acuity with a +3.25D. sph. was: O.D., 20/50; O.S., 20/40. The growth was removed from the right lid and examined histologically and bacteriologically. On July 30, 1937, this lid was given X-ray treatment, 500 r. This was repeated three weeks later.

The patient was not seen by me again until 19 years later. During this interval she had no treatment although the growths had soon returned on both lids. Examination on June 22, 1956, showed on each upper lid a growth similar to that described (fig. 1). The visual acuity of each eye was unchanged; the binocular acuity with glasses was 20/30—. July 2, 1956, both growths were abscissed. Material from them injected into guinea pigs produced no effects. Smears and cultures showed no fungi. Cultures grew out only hemolytic Staphylococcus aureus. By July 31, 1956, both growths had recurred. Thermal cautery was applied to the one on the left lid.

On January 9, 1957, each upper lid showed a growth similar to that removed six months previously. Each growth was again abscissed by one snip of the scissors. In spite of instillation of pontocaine, the abscission caused considerable pain. Hemorrhage was abundant but was easily controlled

ported by Castroviejo,[6] that of a woman ... the cornea may become ulcerated, and even

by slight pressure. June 3, 1957, the patient writes that the growths returned within three days, and that within a month they were as large as ever. "At the present time there is only slight discomfort in the form of itchiness and mucus appearing in the corners of the eyes, especially the left one. Bright sun or lights seem to irritate my eyes." The patient was married over 15 years ago and her only child, a son, has had no ocular disease and so far as she knows none of her relatives, including her parents, a sister, and a brother, has ever had any serious ocular disease.

Discussion

Histologic examinations were made of the excised growths in 1937 when of three months' duration, in 1956 when of 19 years' duration, and in 1957 when of six months' duration. Microscopically all of the specimens show substantially the same picture. The growth is composed chiefly of hyaline connective tissue (fig. 2). In what is evidently the older portion, the tissue consists of large hyaline masses with almost no blood vessels and few stromal cells between them.

Near the surface the hyaline masses become small and the stromal cells abundant. Here more blood vessels are encountered, but they are not numerous. They are small and thin walled, so that veins are not easily distinguished from arteries. At the base, the tissue has the appearance of ordinary granulation tissue. Here there is considerable infiltration with lymphocytes and plasma cells, and occasionally with pus cells. In one small area, eosinophiles are abundant, but in general they are scanty.

In only a few places is epithelium still present over the growth (fig. 2). Elsewhere, apparently, it together with a thin layer of connective tissue has been scraped off artificially. Isolated in the growth are a few foreign body giant cells, some of them enclosing foreign bodies.

At least one cilium is found within the growth. This is not surrounded by giant cells and is evidently not producing any reaction. The cause of the eosinophile is obscure, but no doubt the giant cells were induced by foreign particles that entered the tissue from the conjunctival sac when the growth was abscissed. No doubt the cilium was incarcerated at this time. (It is significant in this connection that Figure 1 shows a cilium lying free on the surface of the growth.)

When first I saw this patient (in 1937), I recalled having seen two similar cases, one in 1905 the other in 1916. The sections and the pathologic reports on these cases are still available but the clinical records have been destroyed. Clinically, all that is certainly known about these cases is that in each the patient was a woman, one age 38 years, that the growth was on the inner surface of an upper lid, and that it recurred when removed. The sections show essentially the same picture as in the present case, except for an extreme abundance of eosinophils in the 1916 case. In the latter case numerous smears and cultures were taken by me and also animal inoculations made, but they did not reveal anything of importance.

From a study of the literature relating to the subject, it is obvious that in the present case and also in my two previous cases, the ocular disease was ligneous conjunctivitis. That this disease is very rare is shown by the facts that in an ophthalmologic experience of 58 years, I have observed no more than three cases, that these were far apart in time, that no one else has reported observing a greater number, and that in the literature I have found no more than 35 cases. It is possible that some cases reported as cases of polypoid tumors or granulomas of the conjunctiva may have really been cases of ligneous conjunctivitis. This is probably true of at least two cases cited from the literature by Elschnig[1] in 1889.

Two especially noteworthy features of the disease are that many more females than males are affected, and that its onset is in childhood. The ratio of males to females affected is more than three to one. The age of the patient at the onset of the disease in the reported cases was, with one exception, under 10 years, and usually under three years. The exception was the case re-

ported by Castroviejo,[6] that of a woman aged 73 years, and this case was exceptional also in so many other respects that I cannot accept it as certainly a case of ligneous conjunctivitis. However, it seems impossible that all adults have acquired complete immunity to this disease.

Goldmann and Hof,[10] in 1954, investigating a case of their own, discovered that their patient belonged to a family which in two generations had five cases of the disease—four females and one male. They therefore concluded that a familial hereditary lowering of resistance played an important role in the disease. In the previous year, without discussing the question of heredity, Paufique and Moreau[8] had cited from the literature seven cases* showing that the disease sometimes affected, in different years, members of the same family, and Winter and Michler[9] had reported the cases of two infant brothers who became affected with the disease at an interval of about one year. These cases, of course, now lend strong support to the conclusion of Goldmann and Hof[10] that the disease is familial.

So far as now known, the disease always begins as a membranous conjunctivitis usually affecting one or both upper lids, but sometimes all four lids. The membrane consists chiefly of fibrin and may cover the entire conjunctiva. It soon shrinks, and when it persists it remains adherent only at a relatively small area. Through this area it becomes organized and largely converted into hyaline connective tissue. Thus the resulting granuloma has a polypoid appearance and is firmly united to the tarsus. The disease may be unilateral throughout its course, but usually it is bilateral. Sometimes it is bilateral only at the onset, soon becoming unilateral because on one side the membrane disappears instead of being organized.[8] In the acute membranous stage of the disease the cornea may become ulcerated, and even perforated. In some cases one or both eyes may be enucleated. In such cases a polypoid granuloma may be formed in the socket.

Preceding and accompanying the membranous conjunctivitis there is usually, if not always, nasopharyngitis, which also may be membranous, and in the girls there is often vaginitis. Although, in some of the reported cases, no mention is made of these conditions, there is nothing said which excludes them. In the acute stage slight glandular involvement may occur, and in severe cases there may be acute glomerulonephritis.

The far greater number of girls than of boys affected with the disease, and the prevalence of vaginitis among the girls, suggest that vaginitis is the usual source of the infection. In the case of a boy, or of a girl free from vaginitis, the source could be the vaginitis of a playmate. I have found no instance of one individual communicating the ocular disease to another.

A remarkable feature of ligneous conjunctivitis is the strong tendency of the membranes and of the granulomas to recur whenever removed. Even when, after abscission, the site is treated with silver nitrate, the actual cautery, or X rays, or it is covered with a conjunctival flap, the granuloma may reform.

Judging by the histologic examinations that have been made, the granuloma after abscission is first replaced by a fibrinous membrane and this becomes organized and converted into hyaline connective tissue, as in the case of the original membrane. However, it is probable that the replacement sometimes occurs without the preliminary formation of a fibrinous membrane. No explanation has been given of the tendency of the granuloma to recur, or of its limitation in size.

The structure of the granuloma suggests a keloid, but my patient (Ruth E.) stated that accidental cuts on her body always healed without leaving protruding scars. In this connection experiments made by Winter and Michler[9] in their two cases may be of

* Evidently by mistake, three of these cases, those of three sisters, were accredited to Franceschetti. Borel,[5] in 1933, had accredited them to Vogt, but I cannot find that Vogt ever published them.

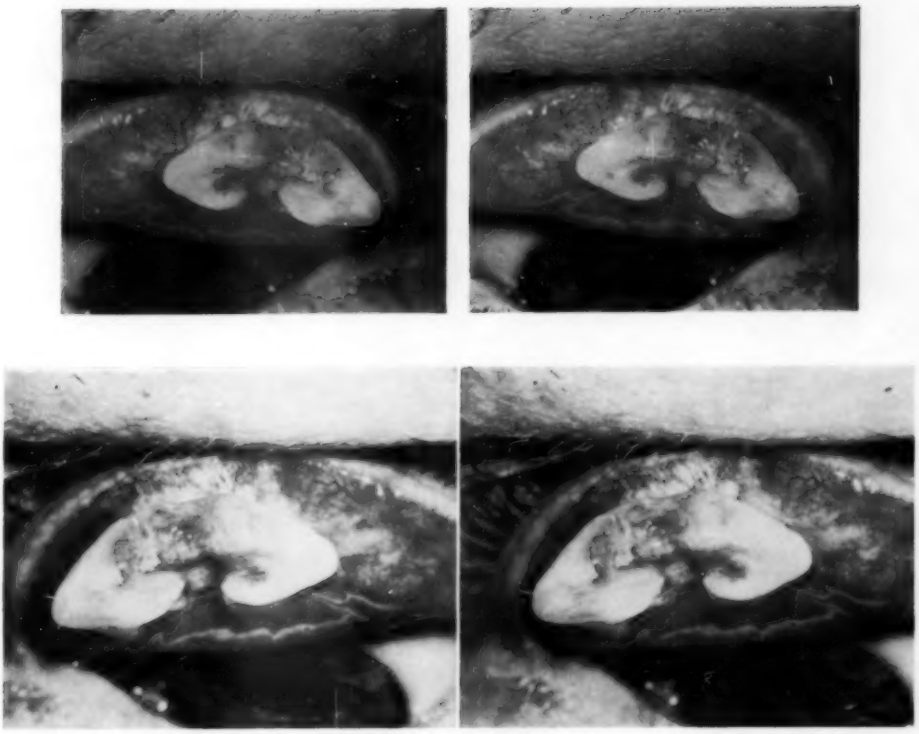

Fig. 1 (Verhoeff). A case of ligneous conjunctivitis now 36 years in duration, showing on everted right upper lid recurrent polypoid granuloma of 19 years' duration. There was a similar granuloma on the left upper lid.
The stereoscopic photograph was taken by Dr. David D. Donaldson on June 22, 1956.

Fig. 2 (Verhoeff). Sections of granuloma (1956), showing hyaline connective-tissue stroma and surface epithelium. Deeper down, the hyaline masses were larger. (Zenker's fixation. Paraffin. Hematoxylin-eosin. ×180.)

considerable significance. They state in regard to one case: "On a recent admission it was found that a membrane could be induced to form in a previously uninvolved area by traumatizing the conjunctiva with forceps." In the other case they obtained the same result by "traumatizing the conjunctiva with carbon dioxide snow (dry ice)."

Dr. Winter reports to me, August 9, 1957, the following additional information. "The fate of the membranes produced by traumatizing the conjunctiva depended to a certain extent on the area traumatized. If the point of trauma was close to the midzone of the upper tarsal conjunctiva of either eye, the membrane produced would persist indefinitely, often gradually fusing and becoming continuous with the indigenous membrane whose stalklike base arose from the midportion of the upper tarsal conjunctiva. If the area of trauma were elsewhere on the upper lid or on the lower lid, the membrane would persist for a matter of several weeks but eventually would regress and disappear."

These experiments suggest that ligneous conjunctivitis depends not only upon an hereditary susceptibility to the original infection, but, in addition, upon an hereditary peculiarity of the palpebral tissue in its response to injury.

As to the duration of the granuloma, or of the period during which it recurs whenever removed, the reported cases give insufficient information. This is so because most of the cases have been reported when the patient was still a child and had been observed for a relatively short time. No case has been reported in which the known duration approached that in my case (Ruth E.), but it seems probable that similar cases have actually occurred. The case with the longest duration previously reported was that of P. Knapp and Roossle.[8] In this case, a uni-

lateral one, the granuloma ceased to recur at the end of six years when it was repeatedly abscissed and the denuded area treated with silver nitrate. In reply to my inquiry, Dr. Winter wrote to me (July, 1957) that in the cases of the two brothers reported by him and Michler[9] in 1953, the granulomas were still persisting and were causing little if any discomfort. These cases, therefore, are now of about the same duration as Knapp's[3] case.

The disease has often been investigated bacteriologically, both in its early and late stages, and no micro-organisms have been found that were believed to be certainly its cause or that of the associated nasopharyngitis or vaginitis. Bacteria such as staphylococci and streptococci, often found, were no doubt secondary invaders. Diphtheria bacilli have been definitely excluded by animal inoculations as a cause for the disease. Since nasopharyngitis is usually due to a filterable virus, it seems almost certain that such a virus is the primary infectious agent in ligneous conjunctivitis and its associated infections. Probably the reason this has not actually been demonstrated to be a fact is that the disease has not yet been subjected to modern methods of virus detection. When identified, the infectious agent may be found to be the cause of a serious type of membranous conjunctivitis not now known to be related to ligneous conjunctivitis.

The acute phase of the ocular disease is self-limited and no medicinal treatment has been found that seems to decrease its severity or shorten its course. Sulfonamides, antibiotics, diphtheria antitoxin, cortisone have all been tried. It is probable, of course, that antibiotics by combating secondary infections may protect the cornea from serious involvement. For the granulomas, as already pointed out, surgical removal is generally ineffective even when combined with treatment of the denuded areas. However, by repeatedly treating the denuded areas by beta rays, Paufique and Moreau[6] have in each of their three cases finally prevented recurrence of the granulomas. The severity of the exposures they employed raises the question as to occurrence of later deleterious effects of the radiation. Certainly such treatment seems inadvisable if the granuloma is causing no serious discomfort as in my present case.

Conclusions

Ligneous conjunctivitis is a familial rare disease which originates in childhood as an acute membranous conjunctivitis and then becomes a chronic condition characterized by at least one persistent palpebral granuloma. The granuloma results from organization of a fibrinous membrane. In the acute stage, by involving the cornea, the disease may seriously impair vision or even cause complete loss of sight.

Associated with the acute stage there is usually, if not always, nasopharyngitis. The primary infectious agent is therefore probably a filterable virus.

There is suggestive evidence that the usual source of infection in this disease is vaginitis of the patient or of some other child.

The present case reveals about the disease three important facts previously unrecorded. First, that in its chronic stage, with a large granuloma on each upper lid, the disease can persist for many years, even for more than 36. Second, that it can do this without affecting vision. Third, that it can do this without ever causing more than trivial discomfort.

Treatment of this disease is unsatisfactory, but in the acute stage antibiotics should be used to combat secondary infection and thus protect the cornea. In the chronic state, if there is only slight discomfort no treatment is necessary. Otherwise, abscissions of the granulomas and applications of beta rays to the denuded areas may be tried.

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DISPUTED PATHOGENESES AND ENTITIES IN UVEITIS*

The XIIth Francis I. Proctor Lecture

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It is a high honor to be asked to deliver the XIIth annual Proctor Lecture and one of which I am deeply appreciative. It is especially pleasant for me, since in my younger days I knew Dr. Proctor personally, honored him for his achievements, and greatly admired him for his dedication to research in ophthalmology. It is also a pleasure to return to the Proctor Laboratory, in the inauguration of which I was privileged to participate, and to witness its great accomplishments in the short space of three years. I extend to Dr. Cordes, to Dr. Hogan, and to their associates, my sincere thanks for this opportunity.

The subject I have chosen for today's lecture, "Disputed pathogeneses and entities in uveitis," is one which I approach with some hesitation. The Proctor Laboratory is one of the great centers for research in uveitis and is distinctly a place where a little knowledge is a dangerous thing! Moreover, I have little original to contribute to the subjects I shall discuss.

There is probably little disagreement on the etiology, pathogenesis, and classification of the two main forms of uveitis, although there may be differences of opinion on nomenclature and other minor points. However, since

> The East is the East, and the West is the West
> And never the twain shall meet . . .

we need not be unduly disturbed over these details.

Suffice to say, it is generally recognized that one form of uveitis is due primarily to an actual infection of the tissues by one of a great variety of pathogens. This group of uveitis I have termed "granulomatous" although others may prefer the term "infectious" or even some more specific appellation. The second form of uveitis is generally believed to be a sterile reaction. To this I have applied the term "nongranulomatous." Many highly competent students may prefer such terms as allergic, toxic, traumatic, or something else. These two general forms

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* From The Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. Delivered at the Department of Ophthalmology, University of California School of Medicine, San Francisco, California, December 6, 1957.

of uveitis and any conflicting opinions about them do not concern us today.

Related to one or both of these recognized forms of uveal inflammation, but with a somewhat individual clinical picture or histology, are a few syndromes about which there is not only some difference of opinion concerning the etiology, pathogenesis, and classification, but in some cases there is question about their very existence as disease entities. I refer to such conditions as lens-induced uveitis, heterochromic iridocyclitis, uveitis associated with collagen diseases other than rheumatoid arthritis, uveitis due to amebiasis, gouty iritis, and diabetic iritis. Today, I should like to discuss two of these, to summarize what is actually known about them, to separate as far as possible the wheat from the chaff, and so endeavor to clarify our thinking. The two topics I have chosen are lens-induced uveitis and heterochromic iridocyclitis.

Lens-induced uveitis

Any dispute over lens-induced uveitis centers on its pathogenesis rather than on its recognition and classification as a disease entity.

Clinically and histologically, two main types of lens-induced uveitis are recognized. These are conventionally termed "endophthalmitis phacoanaphylactica"[1] and "phacotoxic uveitis,"[2] each term implying a specific etiology and a specific pathogenesis. A third type of lens-induced ocular disease—phacolytic glaucoma—is not pertinent to this discussion, for it has been shown[3-4] that the glaucoma is secondary to a blocking of the trabeculae by macrophages laden with phagocytized lens material (fig. 1) and that it may occur independent of any uveitis. A supposed third form of uveal inflammation has been described[5]—uveitis with glaucoma in the second unopened eye with a mature or hypermature cataract which may occur months after an extracapsular extraction on the fellow eye. The similarity and possible relationship of this uveitis to sympathetic ophthalmia has been pointed out and well emphasized by deVeer[6] and others.[7-9] However, since the lens-induced uveitis in the second unoperated eye follows the clinical and histologic pattern

Fig. 1 (Woods). Phacolytic glaucoma. Macrophages blocking trabecular spaces at angle of anterior chamber.

TABLE 1

REPORTED CASES OF LENS-INDUCED UVEITIS IN SECOND EYE AFTER OPERATION OR TRAUMA TO FELLOW EYE

Author–Year	Clinical				Histologic			
	No. of Cases	Postoperative Course in First Eye		Clinical Diagnosis	No. of Cases	Postoperative Course in First Eye		Histologic Diagnosis
		Uneventful	Complicated			Uneventful	Complicated	
deVeer 1940	3	0	3	Sympathetic ophthalmia	3	0	3	Combined picture E.P.A. and S.O.
Courtney 1942	7	5	2	Endophthalmitis with glaucoma	1	1	0	Phacotoxic response
Morgan 1947	5	1	4	Atypical sympathetic ophth.?	3	1	2	Phacotoxic response
Irvine 1952	2	1	1	Phacogenetic uveitis	2	1	1	Phacotoxic response
Haik 1952	1	0	1	Sympathetic ophthalmia	1	0	1	Phacotoxic response
deVeer 1953	3	0	3	Sympathetic ophthalmia?	3	0	3	E.P.A. (2 in exciting, 1 in 2nd eye)
Law 1953	6	2	4	Allergic response lens prot.	0	0	0	———
McDonald 1954	5	3	2	Allergic response lens prot.	0	0	0	———
Leigh 1955	6	3	3	Allergic response lens prot.	2	1	?*	E.P.A. = 1 Phacotoxic response = 1
	38	15	23	Allergic response = 24 Sympathetic ophth. = 12 Phacogenetic uveitis = 2		4	10	E.P.A. = 4 Toxic response = 8 E.P.A. and S.O. = 3

* No note of postoperative course in one case of E.P.A.

of either endophthalmitis phacoanaphylactica or phacotoxic uveitis, it need not be discussed as a separate entity. Table 1 gives a synopsis of the reported cases of this form of uveitis, and its relation to inflammation in the fellow eye.

The question under dispute is whether endophthalmitis phacoanaphylactica and phacotoxic uveitis are two distinct pathogenetic disease entities, or whether they are both caused by the same factor—being either manifestations of a hypersensitivity to lens protein or the result of some irritative or toxic substance elaborated by normal, cataractous, or degenerating lens material.

In the search for an answer to this question, the following points must be considered.

A. The clinical and histologic pictures of the two supposed entities.

B. The evidence for a hypersensitivity pathogenesis.

C. The evidence for a toxic pathogenesis.

D. The significance and evaluation of this evidence.

A. The clinical and histopathologic pictures*

Endophthalmitis phacoanaphylactica

The recognized precipitating factor is some operative procedure or trauma which permits lens material to enter the anterior chamber in eyes already sensitive, or which later become sensitive, to lens protein. If the tissues are already hypersensitive, the onset of symptoms is early, beginning a few hours after the primary injury. If the tissue hypersensitivity develops only after the lens material is liberated in the anterior chamber, the onset of symptoms will be delayed and usually begins from the eighth to the 14th day.

After either an early or delayed onset, there is a rapid development of acute in-

* The following description of the clinical and histologic pictures of endophthalmitis phacoanaphylactica and phacotoxic uveitis are based on the descriptions in the literature, the material available in the Wilmer Institute, and slides from the Armed Forces Institute of Pathology kindly furnished by Dr. Lorenz E. Zimmerman.

Fig. 2 (Woods). Polymorphonuclear cells around traumatized lens fibers in endophthalmitis phacoanaphylactica (high power).

Fig. 3 (Woods). Leukocytes, palisading epithelioid cells, fibroblasts, nongranulomatous inflammation in endophthalmitis phacoanaphylactica (low power).

flammation, with ciliary congestion, clouding of the cornea, edema of the iris, a sero-fibrinous exudate in the anterior chamber, and the formation of fibrinous posterior synechias—the picture of a severe, complicated nongranulomatous iridocyclitis. In addition to this, however, heavy lardaceous, mutton-fat deposits form on the endothelial surface of the cornea—a finding characteristic of the granulomatous form of uveitis. The subsequent course of the endophthalmitis is prolonged and chronic, often with the final formation of a cyclitic membrane, again suggestive of granulomatous uveitis.

Histologically,[1, 2, 6, 7, 10] the maximum reaction is at the point of rupture in the lens capsule or where the extravasation of the lens material is greatest. Here there is a collection of polymorphonuclear neutrophils and often some eosinophils around the traumatized lens fibers (fig. 2). Beyond this center there are usually masses of epithelioid cells, sometimes arranged in palisades. The outermost zone is fibrovascular tissue, and beyond this there is cellular infiltration by lymphocytes and plasma cells (fig. 3). The lardaceous keratic deposits are composed of masses of macrophages and epithelioid cells (fig. 4). Eosinophils may be present, sometimes in abundance. Ashton (personal communication) believes these are almost characteristic. In addition to this granulomatous reaction around the lens material, there is a concomitant classical nongranulomatous uveitis in other parts of the eye. This is characterized by a sero-fibrinous exudate and cellular infiltration of the tissues with lymphocytes and plasma cells (fig. 5). In short, the histologic changes, like the clinical picture, are those of a mixed nongranulomatous and granulomatous uveitis.

Phacotoxic uveitis

This may follow an operative or traumatic insult or may occur in an unopened

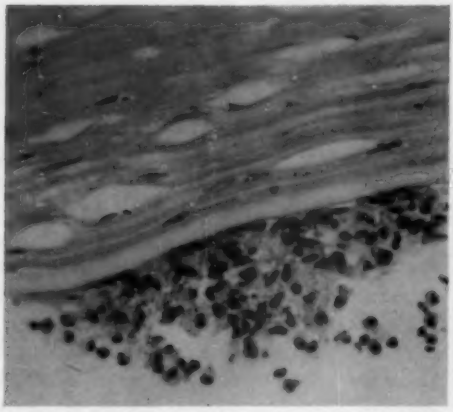

Fig. 4 (Woods). Lardaceous keratic deposit in endophthalmitis phacoanaphylactica.

eye with a hypermature lens where an increased permeability or a rupture of the lens capsule permits lens material to seep into the ocular chambers.

Clinically, phacotoxic uveitis may vary from a mild or moderate postoperative or posttraumatic iridocyclitis with either a few or no keratic deposits up to a severe nongranulomatous uveitis. The severe form may sometimes have the remarkable and confusing added feature of heavy lardaceous, keratic deposits which sharply suggest a granulomatous process.

Histologically, the only human material available for study is from eyes in which the inflammation was so severe that enucleation was performed. These eyes have shown a generalized nongranulomatous inflammation of the iris and ciliary body, with lymphocytes and plasma cells infiltrated through the anterior uvea (fig. 6) and a serofibrinous exudate with plasma cells around the ciliary processes (fig. 7). In the severe cases, the same eye with this nongranulomatous re-

Fig. 5 (Woods). Nongranulomatous reaction in iris remote from traumatized lens fibers in endophthalmitis phacoananphylactica.

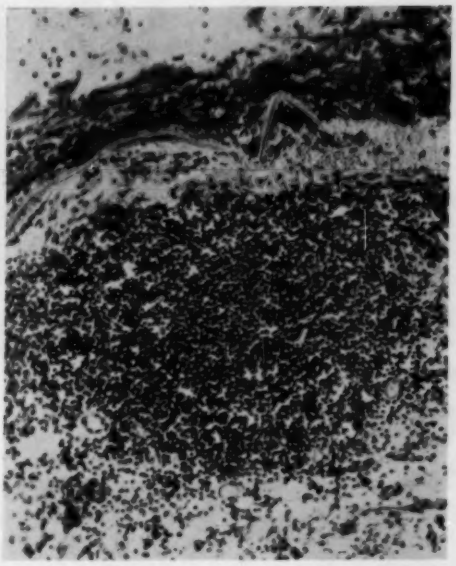

Fig. 6 (Woods). Generalized nongranulomatous reaction in phacotoxic uveitis. Nodule of lymphocytic and plasma cells in ciliary region.

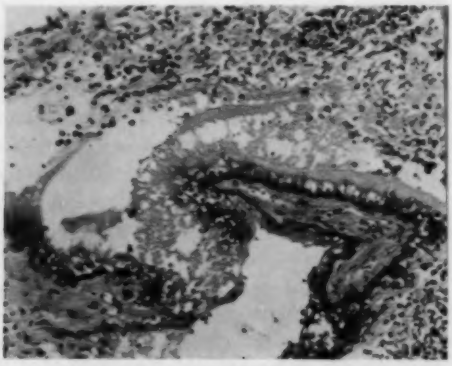

Fig. 7 (Woods). Serofibrinous exudate and plasma cells around ciliary processes.

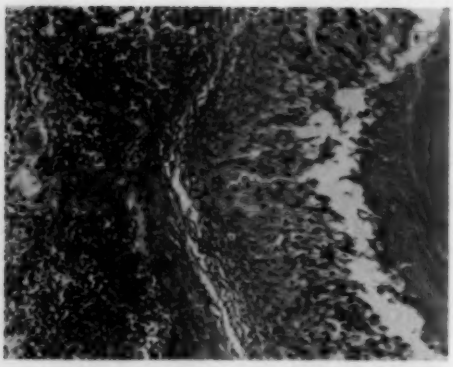

Fig. 8 (Woods). Macrophages and palisading epithelioid cells in phacotoxic uveitis.

action may also show macrophages swollen with phagocytosed lens material in the ocular chambers, and around the disintegrating lens fibers masses of epithelioid cells, often arranged in palisades. Around this there is usually more or less fibrovascular tissue, and beyond there lies the nongranulomatous reaction, often with nodules of lymphocytes and plasma cells (fig. 8). Few or many eosinophils may be present. In short, with the exception of the absence of neutrophils immediately in contact with degenerating lens fibers, the picture is similar to that of endophthalmitis phacoanaphylactica.

B. The evidence in favor of a hypersensitivity pathogenesis

What is the evidence that either one or both of these two forms of lens-induced uveitis are hypersensitive phenomena?

In 1903 Uhlenhuth[12] discovered an organ-specific property in lens protein; that is, there is some protein constituent in the lens which differs antigenically from the other proteins of the body. This constituent lacks species-specificity; that is, it is antigenically the same irrespective of the species from which the lens is derived. Most important, it is capable of acting as an antigen in the homologous animal.

Other investigations in many European and American laboratories[13] have confirmed the basic validity of Uhlenhuth's discovery. These various investigations also demonstrated that whole lens protein was a very weak antigen, and that although heterologous lens would produce precipitins in the experimental animal, it was difficult, and frequently impossible, to produce the Arthus type of sensitivity by the injection of the lens protein alone. It was further found[14] that the alpha crystalline was the globulin fraction of lens protein responsible for its organ-specific antigenic property.

In 1934, Burky[15] discovered the synergistic action of antigens, that when a strong antigen is used in conjunction with a weak one, the antigenic activity of the latter is enhanced. By combining lens protein with staphylococcus toxin, Burky was finally able to produce in rabbits the Arthus type of sensitivity to lens protein and, by the later discission of the lenses of these animals, to produce an anaphylactic nongranulomatous endophthalmitis. This reaction, however, lacked to some degree the neutrophilic response believed characteristic of human endophthalmitis phacoanaphylactica. This finding has since been confirmed.[16] Thus it appears that not only does lens protein possess the antigenic property necessary to make the hypersensitive hypothesis tenable, but that there is also experimental evidence to support this theory.

In 1922, the classical paper of Verhoeff and Lemoine on endophthalmitis phacoanaphylactica appeared. These authors reported clinical studies on 11 patients who were hypersensitive to lens protein and all of whom developed a severe, apparently sterile, endophthalmitis after extracapsular cataract extractions or traumatic rupture of the lens capsule. Five of these eyes were enucleated and all showed what was believed to be a characteristic histologic picture. These observations and further experimental studies convinced these investigators that this postoperative or posttraumatic reaction was a true anaphylactic inflammation produced in hypersensitive individuals by absorption of

their own lens material. Verhoeff and Lemoine also suggested that the uveal inflammation so often observed in children after a second discission could be explained on this same basis.

Various other investigators[11, 15, 17, 18] now explored the occurrence of hypersensitivity to lens protein in cataractous individuals. All of these reports indicated that anywhere from eight to 17 percent of these patients were hypersensitive. With the single exception of Gifford, these investigators all reported that when these hypersensitive patients were later operated on for cataracts, they ran stormy postoperative courses if any lens material was left in their eyes. One of these hypersensitive patients was desensitized with lens protein prior to operation, and thereafter ran an uncomplicated course after an extracapsular extraction.

There is also some evidence that patients with a histologically proven phacotoxic reaction may at least occasionally be hypersensitive to lens protein. In 1942 Courtney reported seven patients with lens-induced uveitis and glaucoma in the second, unoperated eye, occurring after extracapsular cataract extractions on the fellow eye some months previously. All of these patients were proven hypersensitive to lens protein. One of these second eyes was enucleated. Histologically, it showed the typical phacotoxic reaction.

The histologic pictures of both forms of lens-induced uveitis are compatible with a hypersensitive pathogenesis. A recent study[19] of the histologic changes produced in hypersensitive eyes by single and repeated allergic and anaphylactic insult has shown that the initial cellular response is an outpouring of neutrophils. These are usually quickly replaced by lymphocytes and their transitional forms of plasma cells. These cells, together with a serofibrinous exudate, gave the picture of nongranulomatous inflammation. In one of these experimental eyes, subjected to repeated insult, there was some persistence of the neutrophils and, in addition, beneath a detached retina, there was a layer of palisading epithelioid cells.

C. Evidence for a lens toxin pathogenesis

What is the evidence that some inherent or developing toxic or irritative property of lens protein may be responsible for at least one of these recognized forms of lens-induced uveitis?

This possibility was brought into sharp focus in 1899 when Schirmer[20] raised the question of whether the inflammatory reactions after cataract extractions were due to low-grade infection or resulted from a toxin in the retained lens material. There was then no clear answer to the question. In 1911, Lagrange and Lacoste[21] discussed these two conflicting views and decided there was still insufficient evidence to justify a decision. However, in the next few years it became evident that the majority of these postoperative inflammations were sterile reactions, and the toxic theory gradually became generally accepted. In 1918 and again in 1927, the elder Gifford[22] suggested that the toxicity of degenerating lens protein was not only the factor responsible for lens-induced uveitis but was also responsible for the glaucoma which frequently accompanied it.

In 1919, there appeared a remarkable report, under Straub's[23] name, on uveal inflammation produced by supposedly toxic cataractous lens material. Straub had died in 1916 and this monograph was compiled by his pupils from notes left by him. In this paper, it was hypothesized that while the lens protein of children and young people was nontoxic, as the lens grew older, and especially if it became cataractous, it became toxic. This hypothesized toxicity was assumed to be the cause of the uveitis which might accompany retained lens material, or would result from a dislocation of the lens, or a rupture of the capsule, or even from spontaneous absorption of a hypermature cataract. The uveitis with glaucoma which

might occur in the second unopened eye after a cataract extraction on the fellow eye was also recognized by Straub. Straub attributed this to some substance which affected the permeability of the capsule and permitted the toxic lens material to seep into the chambers of the second eye. The histologic picture of what was later described and recognized as endophthalmitis phacoanaphylactica with the characteristic neutrophilic response was described in this paper. Either Straub or his pupils gave to this entity the name of "endophthalmitis phacogenetica." Various clinical observations were also reported, all of which could be logically explained on the basis of a toxicity in the cataractous or hypermature lens.

This monograph was written in Dutch and apparently was never fully translated and published in English. However, extensive reviews appeared in the various ophthalmic journals and these had a profound effect on current ophthalmologic thought. Despite the circumstantial nature of the evidence presented, the absence of any direct experimental proof that cataractous lens material was toxic, and the somewhat far-fetched nature of some of the assumptions, this report appeared to remove any lingering doubts about the toxicity of cataractous lens protein and was convincing to no less a person than the late Sanford Gifford.

The toxicity of cataractous and hypermature lens protein was now so firmly accepted that, in 1922, Elschnig,[24] in this article in the Graefe-Saemisch Handbuch, stated flatly that hypermature lens protein was irritating. Verhoeff and Lemoine also stated that ocular inflammation might follow the rupture of the capsule of a morgagnian cataract, that this inflammation was due to irritation from the disintegrating lens protein, and was analagous to that produced by any necrotic material.

In 1925, Gifford[11] reported a clinical, histologic, and experimental study on the allergic and toxic properties of lens protein. While he found many cataract patients were hypersensitive to his preparations of lens protein, he observed little difference in the postoperative courses of the positive and negative reactors. He reported eight patients who were insensitive to lens protein and who showed postoperative reactions which varied from a mild iridocyclitis of two weeks' duration which cleared with 20/20 vision, up to a severe uveitis which progressed to phthisis and enucleation. This last eye showed histologically a round-cell infiltration of the tissues and also keratic deposits.

To support the hypothesis that these cases were due to some toxicity of lens protein, Gifford pointed out that many protein split products were toxic, that enzymes capable of splitting lens protein had been found in the aqueous and in the cataractous lenses. He then attempted to produce uveitis in experimental animals by a hypersensitive mechanism, but was unsuccessful. Other experiments convinced him that there was an inherent toxicity in lens protein, which was more marked in cataractous lenses.

Gifford did not discard endophthalmitis phacoanaphylactica as an occasional clinical entity, but was convinced that some toxic property of lens protein was the most important factor in this postoperative inflammation after cataract extractions. It should be emphasized, however, that Gifford did not demonstrate, isolate, or identify any toxic component in either normal, cataractous, or hypermature lens protein.

Later observations by other investigators indicated that lens emulsion is an excellent culture medium and that if it becomes contaminated during any stage of its preparation, even though sterile when finally used, it is usually irritating or toxic when injected in the eyes of normal rabbits or the skin of patients. If the emulsions are prepared under rigidly sterile conditions, the resulting preparations will be nonirritating and nontoxic. Gifford's results may therefore have been due to the method used by him to prepare emulsions of lens protein. The failure of his hypersensitivity experiments was almost un-

doubtedly due to the fact his animals did not possess the necessary Arthus type of sensitivity, the synergistic action of antigens, by which such sensitivity is produced, being unknown in 1925.

There were a few protests against this supposed toxicity of lens protein. In 1927, Arnold Knapp[25] took sharp exception to the views expressed by Elschnig and by the elder Gifford and stated that in his large operative experience he had found morgagnian cataractous material nontoxic and nonirritating. A quick survey of the postoperative courses of patients in the Wilmer Institute who were subjected to extracapsular extractions of morgagnian cataracts and whose eyes were, therefore, flooded with morgagnian fluid, confirmed Knapp's observation. In 1952, Müller[26] reported an extensive study of lens-induced uveitis. In his experiments, he filled the anterior chambers of the eyes of normal rabbits with emulsions of homologous and heterologous lens material in "various stages of digestion." He observed no dramatic reactions to such injections and could find no evidence for a toxicity in degenerating lens protein.

Despite the fact that the toxicity of degenerating lens protein was unproven, it continued to be generally assumed that such a hypothesized toxicity was the actual cause of lens-induced uveitis. Heath,[27] in 1941, and Sugar,[28] in 1949, writing on lens-induced glaucoma, accepted the toxicity of degenerating lens protein as an established fact, as did the Irvines in 1952 and Leigh in 1955, even though the latter inclined strongly to the hypersensitive theory.

The possibility that patients with the phacotoxic form of lens-induced uveitis might be hypersensitive to lens protein has been somewhat neglected by the advocates of a toxic pathogenesis. This point was carefully considered by Gifford in 1925, and by Macdonald[29] in 1954, and was mentioned by the Irvines in 1952. DeVeer, Law,[30] and Leigh all stressed the importance of routinely testing all patients with either form of lens-induced uveitis for hypersensitivity to lens protein since it was only by such a procedure that the question of an anaphylactic or toxic pathogenesis could be solved. Nevertheless, this most important point appears to have been neglected by the majority of investigators in this field. As a result, there is considerable uncertainty as to whether patients with phacotoxic uveitis are hypersensitive to lens protein.

The histopathology of phacotoxic uveitis is compatible with a toxic pathogenesis. Numerous studies, beginning with those of Guillery,[31] in 1914, have shown that the response of the eye to toxins and irritants is essentially a nongranulomatous reaction with a cellular response of lymphocytes and plasma cells. If the toxin is in sufficient concentration, there will also be an outpouring of neutrophils and even tissue necrosis.

D. The significance of the evidence

One confusing point in the above evidence is the occurrence of heavy lardaceous keratic deposits in endophthalmitis phacoanaphylactica and phacotoxic uveitis, and their absence in phacolytic glaucoma. These deposits are composed of clumps of mononuclear monocytes and epithelioid cells, which are attracted to the anterior chamber in all three types of lens-induced ocular disease. Flocks, Littwin, and Zimmerman have suggested that the explanation of this anomaly may lie in the fibrinogen content of the aqueous. The Irvines[2, 32] have shown that in any form of anterior uveal inflammation the fibrinogen content of the aqueous is greatly increased. Thus, in endophthalmitis phacoanaphylactica and the phacotoxic form of the disease, where there is a concomitant nongranulomatous uveitis, a high fibrinogen content in the aqueous would cause the macrophages and epithelioid cells to become "sticky," to clump together, and so result in the keratic deposits and the apparent granulomatous changes around the lens and in the extratissue exudates.

In phacolytic glaucoma, where there is

no concomitant uveal inflammation, the fibrinogen content of the aqueous would be low, the cells would not become sticky but would remain free in the aqueous, to be wafted to the angle and there block the trabecular spaces. This same reasoning gives a ready and logical explanation for the apparent granulomatous changes so frequently present in both forms of lens-induced uveitis.

The mononuclear macrophages and their transitional epithelioid cells are usually considered almost pathognomonic of granulomatous disease and are responsible for the granulomatous appearance seen in endophthalmitis phacoanaphylactica and sometimes in phacotoxic uveitis. However, they are apparently in no way related to these basic uveal inflammations. In all forms of lens-induced ocular disease these macrophages are mustered in the anterior chamber to perform their routine duty of policing up the premises—in these instances to phagocytose any liquid or particulate lens material. When there is a concomitant nongranulomatous uveitis present with an increased fibrinogen content of the aqueous, these cells clump together to give a false appearance of granulomatous disease, and so account for the "mixed" type of the uveitis. Since they are not attracted to the eye by the uveal inflammation itself, they can therefore be disregarded in a consideration of the pathogenesis of both forms of lens-induced uveitis.

When the lardaceous, mutton-fat keratic deposits are explained on the above basis, the existing evidence indicates that both forms of lens-induced uveitis have certain points in common and one particular point of difference. The points of similarity are that both have a common etiology, that is, the local absorption of lens protein. In both the onset may be early or delayed. In both a part of the histologic picture is a generalized nongranulomatous uveitis and part is a localized granulomatous reaction. The chief point of difference is that in endophthalmitis phacoanaphylactica there is a mobilization of neutrophils around the disintegrating lens fibers while in the phacotoxic uveitis these cells are relatively or completely absent.

If a common pathogenesis is attributed to these two forms of lens-induced uveitis, this discrepancy in the histologic pictures must be explained. If both forms of this uveitis are hypersensitivity phenomena, in endophthalmitis phacoanaphylactica it may be reasoned that the prolonged absorption of the antigen results in a persistence of the initial leukocytic cellular response, with resultant mobilization and persistence of the neutrophils around the traumatized lens fibers. But if this is true, why does not a similar reaction occur in phacotoxic uveitis, where there is also slow and prolonged absorption? Possibly the degree of tissue hypersensitivity and the intensity of the anaphylactic insult may be the answer. The possibility of a low-grade infection in some cases of endophthalmitis phacoanaphylactica cannot be completely dismissed even though there is no evidence in favor of such an assumption. If a toxicity of lens protein is believed to be the responsible pathogenic factor, it is possible that differences in the potency and concentration of the hypothesized toxin are responsible for the difference in the cellular response. Until this question is clarified, the possibility of different pathogeneses cannot be dismissed.

It would, however, seem improbable that two such similar clinical conditions, often merging one into the other and both stemming from the common etiologic factor of absorption of lens protein, should have such radically different pathogeneses. If any of the above explanations for the presence and absence of neutrophils can be accepted, can the other manifestations of these two forms of lens-induced uveitis be explained on the basis of a single pathogenesis?

If both are viewed as hypersensitive inflammations, the early or delayed onset would depend on whether the tissues were already hypersensitive to lens protein, or whether they later became so from absorption of the lens material liberated in the anterior cham-

ber. If the latter, the delayed onset would be analogous to that of ordinary serum sickness. The nongranulomatous inflammation seen in both types is the usual reaction to anaphylactic insult.

In endophthalmitis phacoanaphylactica, the mobilization of neutrophils around the disintegrating lens fibers can be explained as the initial cellular response to an antigenic stimulus which is prolonged on account of the slow absorption of the lens protein. The surrounding pseudogranulomatous reaction is due to the macrophages attracted to the eye by the extravasated lens material and so may be similar to the reaction provoked by necrotic collagen, or occurring around a rheumatic nodule, but here is centered around disintegrating lens tissue. The rapid recovery which follows complete removal of the lens or residual lens material is due to the removal of the antigenic source. The case for the adherents of a hypersensitivity pathogenesis may therefore be summed up as:

1. Lens protein possesses the necessary antigenic properties to make the hypersensitivity pathogenesis tenable.
2. All patients with endophthalmitis phacoanaphylactica and at least some patients with the phacotoxic reaction are hypersensitive to lens protein.
3. The clinical symptomatology and histologic changes of both forms of lens-induced endophthalmitis can be explained as hypersensitive phenomena.
4. The removal of the antigenic source is followed by a subsidence of symptoms.
5. In the experience of many observers, morgagnian lens material is not toxic.

If both forms of lens-induced uveitis are viewed as toxic reactions, the hypothesized toxicity of cataractous and hypermature lens material must first be conceded. Once over this hurdle, the balance of the explanation is easy. The early or late onset of symptoms would depend on a toxicity already present in the liberated lens material or on one later developing as the lens protein disintegrates. The nongranulomatous inflammation present in both forms of the uveitis is the usual reaction to a toxic insult. The mobilization of neutrophils around disintegrating lens fibers in endophthalmitis phacoanaphylactia is the purulent reaction stimulated by a strong toxin and is greatest where the concentration of the toxin is most intense. The surrounding granulomatous reaction is the usual response to degenerating and necrotic material. The rapid recovery which occurs after removal of lens material is due to getting rid of the source of the toxin.

The case for a toxic pathogenesis may, therefore, be summed up as:

1. The tradition of toxicity in cataractous and hypermature lens protein.
2. The clinical symptomatology and histologic changes of both forms of uveitis can be accounted for on the basis of a toxic pathogenesis.
3. The removal of the toxic lens or lens material is followed by a subsidence of all symptoms.

From this briefly summarized evidence, it appears that those who would explain both forms of lens-induced endophthalmitis as hypersensitive phenomena have somewhat the better of the argument. But the case is far from closed. Although somewhat improbable, it may be that the two clinical types of lens-induced uveitis are pathogenetically distinct entities. If the advocates of the hypersensitivity theory can demonstrate a specific antigen-antibody reaction to the alpha crystalline (the organ-specific constituent of lens protein) in the eyes of patients with the phacotoxic form of the disease, they would cement their case. This may ultimately be possible by the Coombs technique.

Similarly, if the adherents to the toxic theory can demonstrate an actual toxicity in cataractous or hypermature lens material, and can prove that the phacotoxic form of the uveitis occurs in individuals who are insensitive to lens protein, they would thus

establish a toxic pathogenesis for this form of lens-induced uveitis.

Until these possibilities are further explored and one or the other is conclusively demonstrated or disproven, the questions of a single pathogenesis or of two pathogenetically distinct entities must remain undecided.

Heterochromic iridocyclitis

To question the position of hereterochromic iridocyclitis as a disease entity savors somewhat of lèse majesté," for Fuchs' syndrome is of noble birth and many brilliant ophthalmologists have worshipped at this shrine for a full half-century. Nevertheless, while the integrity of this syndrome as a clinical entity is not challenged, it is permissible to ask what criteria are necessary to promote a clinical syndrome to the rank of a disease entity. If a distinctive combination of objective symptoms is sufficient, then there is little more to be said. However, if one demands further supporting evidence, such as an individual histopathologic picture not shown by other disease entities, or an established specific etiology, then even a time-honored syndrome such as heterochromic iridocyclitis requires examination of its clinical picture, histopathology, and possible etiology before it can be given recognition as a separate disease entity.

The association of pigmentary changes with cataract was noted by Jonathan Hutchinson in 1869.[33] Thereafter there are numerous casual references in the literature on the occurrence of heterochromia iridis in patients with uveitis. In 1906, Fuchs'[34] classical paper on this subject appeared and since that time the combination of symptoms described by him has been known as "Fuchs' syndrome," or heterochromic iridocyclitis. Since this original description there have been many reports on various phases of this syndrome, one of the most recent being from the Proctor Laboratory[35] with excellent pictures and lucid descriptions of the clinical symptomatology and histopathology. The clinical and histologic pictures of this Fuchs' syndrome and the story of the various suggested etiologies may be summarized as follows:

Clinical picture

The available figures indicate that Fuchs' syndrome may occur at almost any age except in infancy. There is, however, an increased incidence in the third and fourth decades. There is no especial race or sex distribution. It is more frequently unilateral than bilateral. Kimura, Hogan, and Thygeson give the incidence in their total uveitis series as about two percent.

The salient features of the syndrome are a quiet protracted iridocyclitis with little or no manifest ciliary congestion or external evidence of inflammation. The iris pattern gradually becomes altered with some atrophy of the peripheral layers, including the dilator fibers and the pupillary border. This thinning of the iris stroma and loss of the normal architecture result in a relative exposure of the pigment layer with the late development of a heterochromia. There is little or no tendency to the formation of posterior synechias. There are small, pinpoint keratic deposits.

Some authors have described a few motile cells in the aqueous, and a weakly positive ray, but others state the anterior chamber is optically empty. In the early stages there may be moving veils in the anterior vitreous, and fine white dots usually adherent to the vitreous framework. These are believed to be of diagnostic importance. Franceschetti believes they result from the condensation of "curtainlike membranes" and may finally form more or less compact veils, suggestive of those which occur in a tuberculous uveitis. Small areas of peripheral focal choroiditis have occasionally been described, but it seems generally agreed that the posterior uvea is not involved.

A slow-forming, secondary cataract is a frequent complication. This is probably due to a nutritional disturbance and occurs in about 13 percent of the cases (Kimura et al.) These eyes frequently develop a late and somewhat intractable glaucoma.

François (1946[36]) and Franceschetti

(1955[37]) have described some neovascularization and indefinite veils at the angle and over the base of the iris. Blocking of the trabecular system by this tissue, a ciliary crisis akin to that of the Posner-Schlossman syndrome, and fibrosis of the trabecular system have all variously been suggested as possible causes of this glaucoma. Amsler and Verrey (1946[38]) noted that patients with this syndrome were especially liable to anterior chamber hemorrhages when subjected to a paracentesis, suggesting an increased capillary fragility. Franceschetti described fine filaments between the small keratic precipitates. The nature of these was not identified, but his description suggests they may have been fibrin.

These various descriptions of clinical symptomatology are compatible with a subacute, chronic nongranulomatous iridocyclitis. However, in 1926, Streiff[39] reported an observation which was later apparently misinterpreted and gave rise to a concept which is somewhat out of harmony with that of a nongranulomatous iritis. Streiff reported a case of heterochromia in which there were small nodular efflorescences at the pupillary edges and over the surface of the pupillary zone of the iris (fig. 9). In the absence of a histologic examination, Streiff at first was unwilling to venture a guess as to their nature. He followed this patient over a two-year period and observed no change in their appearance, and was finally inclined to the opinion they were not inflammatory, but were a congenital anomaly.

Vogt,[40] in his 1941 *Atlas* (plate 1738), described similar efflorescences in a patient with heterochromia, an iridocyclitis, and a concurrent latent syphilis. Under the heading, "Rare form of iritis with flaky precipitates on the anterior surface of the iris in suspected heterochromic iridocyclitis," he further reported two other cases, in one of which he described these efflorescences as a "bluish, flaky deposit right around the pupillary border . . . and strewn on the mesoderm of the brown iris." These efflorescences became irregular and apparently slightly pigmented over an eight-year period of observation.

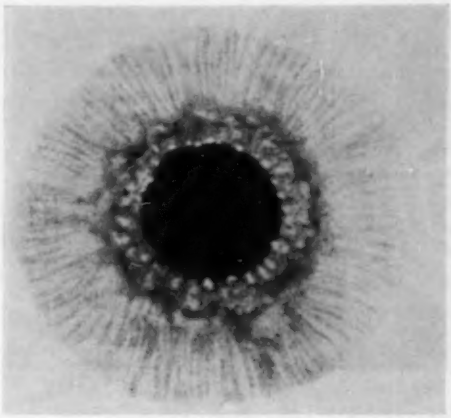

Fig. 9 (Woods). Iris nodules in a case of heterochromia (Streiff, 1926).

Franceschetti (1955) described what are apparently similar nodules as "ephemeral nodules" at the pupillary border and stated they occurred in about one third of the cases of heterochromic iridocyclitis. Strangely enough, these nodules were apparently not observed in any of the cases reported by Kimura, Hogan, and Thygeson.

It is difficult to reconcile these various reports. It is undoubtedly true that occasionally in the chronic type of nongranulomatous iridocyclitis small ephemeral flaky deposits occur at the pupillary edge and on the iris surface. Superficially they suggest Koeppe nodules. They may completely absorb or shrivel up and become slightly pigmented. They may occur in eyes without any heterochromia (JHH, case 309710). From their appearance and course, they suggest coagulated fibrin, and it is well known that in all forms of anterior uveal inflammation there is an increased fibrinogen content of the aqueous.[32]

The possibility that some of these efflorescenses may in truth be Koeppe nodules is suggested by a comparison of the pictures of these nodules in the 1941 edition of Vogt's Atlas with Figure 315-A and B in the 1921 edition of the same Atlas. In the latter, quite

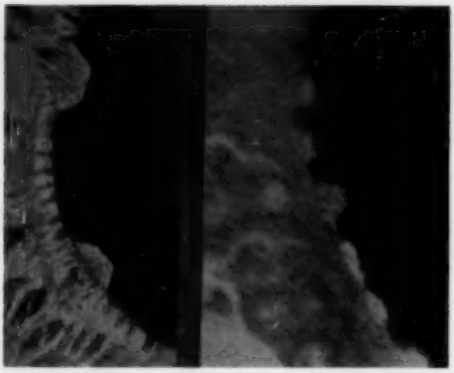

Fig. 10 (Woods). (Right) Tubercles of the iris (Vogt, 1921). (Left) Iris nodules in heterochromic iridocyclitis (Vogt, 1940).

similar nodules are entitled "Tubercles of the iris" (fig. 10). These ephemeral nodules occur in various forms of low-grade chronic granulomatous uveitis.

Franceschetti recognized this similarity of the nodules he observed in heterochromic iridocyclitis to those which occur in tuberculous uveitis, but believed they could be distinguished by their morphology. However, anyone who has carefully watched the changing appearance of Koeppe nodules as they form, gradually shrivel, undergo absorption, or occasionally organize and become slightly pigmented, will find difficulty in attaching much diagnostic importance to alterations in their morphology. It is therefore possible that the efflorescences described in heterochromic iridocyclitis may be either coagulated fibrin or possibly Koeppe nodules occurring in a low-grade chronic granulomatous iritis with a secondary heterochromia.

Pathology

In his 1906 paper, Fuchs described the histopathologic picture as cellular infiltration of the iris with lymphocytes, plasma cells, and eosinophils. There were also hyaline changes in the media of the arterioles. In his 1917 paper,[41] he described one case as having the histologic picture of nonspecific inflammation. His second case with unilateral heterochromia iridis was confusing. Both eyes were obtained at autopsy, and the eye with the heterochromia and the one with the normal iris color both showed the same picture of nonspecific inflammation, but there were also clumps of epithelioid cells around Schlemm's canal. Fuchs evidently suspected tuberculosis because he stained the sections for bacilli but did not find them.

Schlippe[42] (1910) reported lymphocytic and plasma cell infiltration of the iris. Franke[43] (1917), François (1946), and Georgiades[44] (1953) reported similar findings, together with hyaline changes of the arterioles. Franceschetti believed these latter changes were primarily degenerative.

Kimura et al. described changes in the stromal melanocytes with fine depigmentation. One of their cases showed a deposition of pigment on the anterior layer of the iris, probably laid down by phagocytes. Their cases showed diffuse fibrosis of the iris stroma and infiltration with lymphocytes and plasma cells. They reported fibrosis of the ciliary body and occasional small areas of focal cyclitis and peripheral choroiditis. One case with absolute glaucoma showed an open angle but there was severe fibrosis of the trabecular network.

Etiology

If heterochromic iridocyclitis is a separate disease entity, obviously it should have a specific etiology. However, efforts to discover and identify such an etiology have been fruitless.

The early theories on etiology were based on the assumption that the late development of the syndrome was related to some previous damage to the melanophores. Thus Weill[45] (1904), two years before the appearance of Fuchs' paper, suggested that some circulatory disturbance in intra-uterine life interfered with the development of the melanophores and later predisposed the eye to cyclitis and cataract. Fuchs (1906) did not accept the idea of a circulatory disturbance and hypothesized that the factor which damaged the melanophores was some unknown toxin which operated during intra-uterine life and in infancy and thus rendered the

eyes susceptible to the later development of the heterochromic syndrome. Heine[46] (1912, 1923) believed that the toxin responsible for the damage to the melanophores, and also for the syndrome, was the result of an acquired postnatal infection somewhat akin to tuberculosis. Suffice to say, no clinical or experimental evidence of any sort has been produced to support any of these theories.

Another group of theories attempted to explain heterochromic iridocyclitis on a neurogenic basis. These theories assumed that both the cyclitis and the heterochromia were dependent upon a sympathetic disturbance. Basically, these theories were founded on Angelucci's[47] finding (1893) that extirpation of the superior sympathetic ganglion was followed by a homolateral depigmentation of the iris—an observation which has since been abundantly confirmed.

The various clinical and experimental studies which might support this theory and indicate some degeneration of the homolateral sympathetic chain were summarized by Bistis[48] (1928) who suggested that the cyclitis and cataract were caused by a protein-rich aqueous which resulted from the serum proteins seeping into the posterior chamber from dilated ciliary vessels which were deprived of their sympathetic innervation.

In more modern times, François[49] (1949) reported interesting pharmacodynamic studies on the pupillary reactions of patients with Fuchs' syndrome. He found some suggestive, but inconclusive, evidence of a sympathetic paresis in these patients, but no evidence of involvement of the parasympathetics.

Seeking the source of this possible sympathetic paresis, Passow[50] (1933) advanced the theory that heterochromic iridocyclitis was related to a neurologic syndrome known as "status dysraphicus." This is believed due to an intra-uterine occlusion of the primary neural cleft and is characterized by various bony changes in the fingers, thorax, and spinal column with neurologic symptoms referable to the sympathetic system. This suggestion was not confirmed and was rejected by later investigators. However, Paufique and Etienne[51] (1949) reported that many of their patients with heterochromic iridocyclitis showed radiographic evidence of a cervical arthrosis or discopathy. While this was confirmed by Georgiades (1953), it was not accepted by Franceschetti who found no undue incidence of such arthrosis in his patients with Fuchs' syndrome.

It is evident that, unless further evidence is produced to support them, all these theories must collapse from their own weight. Kimura and his associates dismissed the subject with the flat statement that the etiology of Fuchs' syndrome is unknown, and that extensive examinations to find a specific etiologic factor are useless because all tests will be negative. One may or may not accept the latter part of this dictum, but certainly the first part is justified. It could well be expanded to include a statement that none of the various experimental investigations on the possible specific etiology of heterochromic iridocyclitis have revealed anything which supports the idea that heterochromic iridocyclitis is a separate and distinct disease entity.

Do the clinical and histopathologic pictures alone justify the recognition of this uveal inflammation as a separate disease entity? If the evanescent nodules described by Vogt and Franceschetti are disregarded, there remains a subacute, chronic, nongranulomatous iridocyclitis with the invariable late development of a heterochromia iridis and the frequent development of secondary cataract and glaucoma. The low-grade inflammatory reaction, the type of keratic deposits, the fine vitreous opacities, the occasional strands of fibrin in the anterior chamber, the secondary cataract and glaucoma are all objective symptoms which may well result from a long-continued, subacute allergic or toxic insult to the uveal tissues. The histopathologic picture of nonspecific inflammation with cellular infiltration by lymphocytes and plasma cells is also characteristic of nongranulomatous uveitis.

The one point in the clinical and histo-

pathologic pictures which makes Fuchs' syndrome distinctive is the constant occurrence of the heterochromia. The relative unimportance of this symptom apparently worried Dr. Kimura and his associates because they suggested a new subdivision—a "heterochromic iridocyclitis without heterochromia." I regret I cannot accept this. To my mind it is too much like a production of "Hamlet" with the Prince of Denmark excluded from the dramatis personae!

Excluding Fuchs' syndrome, there are four recognized types of heterochromia iridis:

The first is the simple, uncomplicated heterochromia of congenital origin.

The second is the already mentioned neurogenic heterochromia due to degeneration of the homolateral sympathetics.

The third is the heterochromia of senescence with thinning and atrophy of the superficial layers of the iris and a lightening of the iris color. Histologically, there is degeneration of the mesenchymal and pigment layers of the iris with hyalinization of the connective tissue and muscular framework, especially at the pupillary border. There is some atrophy of the vascular layer with hyalinization of the media and narrowing of the lumen of the vessels. This vascular change is quite similar to that so often reported in Fuchs' syndrome.

The fourth type of iris depigmentation is the secondary heterochromia which may follow any prolonged uveal inflammation. If it follows a granulomatous type of the disease, there are usually associated organic changes referable to the uveitis. If it follows a low-grade nongranulomatous uveitis, there may be no clinical evidences of a present or preceding uveal inflammation. Histologically, if the pathologic changes directly referable to the uveitis are excluded, the picture of this secondary heterochromia is much the same as that of the heterochromia of senescence. The reaction of the iris to the insult of age and to that of inflammation are much the same!

Is there anything in the heterochromia of Fuchs' syndrome which differentiates it from the ordinary secondary heterochromia which may follow any form of prolonged uveal inflammation? Dr. Kimura and his associates believe that the heterochromia of Fuchs' syndrome is a uniform change involving the entire iris while in the secondary type the heterochromia is patchy in distribution. I will agree that both the atrophy of the iris and the pigmentary degeneration which may follow the granulomatous form of uveitis are often patchy in distribution and may involve only a sector of the iris. But, in my experience, the pigmentary change in the iris which may follow a prolonged, subacute, chronic or recurrent nongranulomatous iridocyclitis is almost invariably uniform and tends to involve the entire iris, especially toward the pupillary edge. To my eye, it is indistinguishable from the pigmentary change which is present in eyes which others have diagnosed as heterochromic iridocyclitis.

Perhaps it is much a matter of semantics. If the term "heterochromic iridocyclitis" is used only to describe a collection of clinical symptoms, there can be no great objection to its use although it appears to be an example of the lamentable habit of dividing a disease entity into endless subdivisions on the basis of minor and unimportant variations in the clinical symptomatology. But if this term is used to imply a cause-and-effect relationship between the heterochromia and the uveal inflammation, it is indefensible. There is not a scintilla of evidence any such relationship exists. Unfortunately, this is the meaning attributed to this diagnosis by a number of inexperienced ophthalmologists.

These are the reasons I have always refused to accept heterochromic iridocyclitis as a disease entity and why the incidence of this diagnosis in my personal uveitis file is exactly zero. However, there can be no great objection to the use of the term "Fuchs' syndrome," other than a natural preference for a nomenclature indicative of the etiology and pathogenesis of a disease rather than for one employing proper names or descriptive of morphologic changes.

If the concept of Fuchs' syndrome as a disease entity is abandoned and it is regarded as a subacute, chronic, nongranulomatous uveitis and its cause is sought in some allergic, toxic, or possibly physical insult, the prognosis becomes less gloomy. Undoubtedly, I have seen many patients in whom, were I less stubborn, a diagnosis of Fuchs' syndrome could well have been made. I have never routinely noted the presence or absence of heterochromia iridis in patients with nongranulomatous uveitis and therefore cannot give the incidence of bacterial hypersensitivity and the results of desensitization in the specific group with an associated heterochromia. However, I firmly believe that, when these patients were examined for a specific bacterial hypersensitivity, not only to stock vaccines but also to suspicious organisms isolated from their own foci of infection, that the majority of them showed a specific hypersensitivity.

It is, of course, true that the demonstration of a systemic disturbance in a patient with uveitis does not establish a cause-and-effect relationship between the systemic condition and the ocular inflammation; but, if there is a specific therapy for a demonstrated and possibly related systemic abnormality, then the patient is entitled to the benefit of a therapeutic trial test.

In some patients with Fuchs' syndrome and a demonstrated bacterial hypersensitivity, specific desensitization will be without effect; but, in many others, it will be sufficiently rewarding to compensate for all the fruitless toil devoted to the unsuccessful cases. Certainly, if the heterochromia of Fuchs' syndrome is regarded as an unimportant, late development in a chronic, low-grade nongranulomatous uveitis, the prognosis is somewhat happier than if the present concept of the syndrome is accepted, and the ophthalmologist and patient are stranded on the hopeless diagnosis of heterochromic iridocyclitis.

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